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"SILO-FILLER'S DISEASE"—A SYNDROME CAUSED BY NITROGEN DIOXIDE

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• *Four patients who entered silos within a day or two after filling with corn silage noted irritating fumes and experienced respiratory symptoms of varying degrees of severity. A period of failure to improve was followed by a period of worsening that ended with death on the 27th and 30th days in two cases. The disease was halted in the other two cases by treatment with prednisone. Intramuscular injections of this drug in 10 mg. doses three times daily were followed by prompt and striking improvement, especially in one case. Chemical evidence showed that the toxic gas was probably nitrogen dioxide, a gas capable of causing early pulmonary edema with subsequent bronchiolitis fibrosa obliterans. The bronchiolitis gives a roentgenogram marked by innumerable discrete nodular densities in the lungs and indistinguishable from that of acute miliary tuberculosis; its nature was verified at autopsy in the two fatal cases. Oxygen gave only symptomatic improvement, and the effects of bronchodilators and antibiotics were only temporary. Prevention of silo-filler's disease depends on adequate ventilation, on means of keeping people and animals from straying into dangerous spaces adjoining a silo, especially during the 7 to 10 days after the silo is filled, and on a wider recognition of the danger.*

The inhalation of irritating fumes encountered in or near freshly filled silos has recently been shown [1] to cause serious and potentially lethal respiratory disease in man. The agent producing this condition is nitrogen dioxide, which is always partially polymerized to nitrogen tetroxide. These two gases are both considerably heavier than air, and both are highly toxic upon inhalation. Since the observation by one of us (T. L.) in September, 1955, of two fatal cases [2] we have attempted to gain a comprehensive view of "silo-filler's disease." This term, as employed in the present report, designates any bronchial or pulmonary condition produced by the inhalation of oxides of nitrogen derived from fresh silage. The pathological changes found at autopsy in lungs and bronchi damaged by this toxic gas vary widely with the amount of nitrogen dioxide inhaled. Correspondingly, clinical findings in the patients differ greatly; it is clear that our meager experience has permitted close study of but one of several different clinical and pathological entities that may be produced by this gas.

The following account is, for the most part, an attempt to describe one form of silo-filler's disease that is, itself, a clear-cut, distinct clinical and pathological entity. Typical bronchiolitis fibrosa obliterans has occurred in four individuals exposed to silage fumes under essentially identical circumstances. Correlation of data derived from a study of the four cases has permitted us to outline the clinical features of this hitherto undescribed syndrome. Two additional instances of silo-filler's disease [1b] have recently been reported, each of which differs greatly from the rather closely similar pattern of our four cases. Yet these two cases clearly belong in the same general category and fit the definition given above. We are led, by these combined pieces of evidence and by a study of the pertinent medical literature, to formulate hypotheses concerning other entities that, together with bronchiolitis obliterans, are to be regarded as clinical types of silo-filler's disease. The future recognition of additional similar cases will require that physicians be aware of the condition as a possibility and also that they be acquainted, in a very general manner, with its basic clinical characteristics.

Although the medical literature contains a number of references [3] to fatal bronchiolitis obliterans resulting from accidental inhalation of nitrogen dioxide in such places as industry and the chemical laboratory, we have been unable to find any record of bronchiolitis in the human caused by exposure to gas or fumes evolved by fresh silage. A probable explanation for the lack of earlier reports is the apparent rarity of this condition; in all likelihood, the production, in a silo, of nitrogen dioxide concentrations sufficient, when inhaled, to cause bronchiolitis depends upon

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a particular and unusual combination of chemical circumstances. Experimental work now in progress should eventually yield much more information concerning these circumstances.

We wish to emphasize the fact that the observations to be reported do not imply need for any change in current silage-making methods. It is our intent, rather,

Fig. 1. (case 1).—Roentgenogram made 25 days after exposure to silage fumes and only 3 days before death. Note confluent infiltration of upper lung fields. The numerous discrete nodules throughout remaining lung tissue are not seen in this reproduction.

to describe a distinct, serious, physical hazard that can readily be avoided and to make the essential data available to physicians generally (especially to those practicing in rural areas) prior to the completion of another growing season. The disease under consideration is a clear-cut, specific entity, not previously described nor recognized as an occupational hazard in agriculture. It produces a striking clinical syndrome. The roentgenographic findings may be indistinguishable from those of other well-established pulmonary diseases such as miliary tuberculosis. A history of recent exposure to irritating silage fumes is the essential evidence that identifies this condition and differentiates it from conditions similar in other respects.

Since certain clinical features necessarily provide the clues that will permit practicing physicians to recognize silo-filler's disease, one of our cases will be described in detail, whereas the remaining case histories will be briefly summarized. The patients in cases 1 and 2 were observed by one of us (T. L.) during the terminal phase of their illness; those in cases 3 and 4 are reported through the courtesy of their respective physicians.

Report of Cases

Case 1.—A 28-year-old farmer climbed an enclosed ladderway to the top of his silo on Sept. 1, 1955, in order to open the top door for purposes of ventilation. The silo had been filled on the previous day with straight corn silage containing no chemical additives. While climbing this enclosed, nonvented ladder, he noticed an irritating odor, accompanied by oppressive heat and humidity that "almost overcame him" and forced him to climb down without accomplishing his intended task. He came down the ladder coughing and weak; he was nauseated but did not vomit. He coughed intermittently and increasingly from the day of exposure onward, wheezed a good deal of the time, was dyspneic on any exertion, and was noted to be weak, tired, and listless. On Sept. 16, 1955, shaking chills and fever were noted and cough and dyspnea worsened; the patient was finally induced to consult his physician on Sept. 21, 1955. He was given treatment for "pneumonia," but two days later all of the symptoms had increased alarmingly; his cough was incessant, and the slightest exertion or movement now caused him to gasp for breath. On Sept. 24, 1955, he entered Glencoe Municipal Hospital, where he was placed in an oxygen tent and received penicillin together with one other antibiotic the administration of which had been started on Sept. 21; his condition deteriorated further, however, and on Sept. 27, his physician consulted one of us (T.L.) by telephone. In accordance with the suggestion of his physician, arrangements were then made for his transfer by ambulance (and with continuous administration of oxygen) to Northwestern Hospital, Minneapolis.

On admission, the patient was in critical condition. Rectal temperature was 102 F (38.9 C), pulse rate 128 per minute, respiratory rate 52 per minute, and blood pressure 170/80 mm. Hg. Dyspnea was extreme; the respirations were rapid, shallow and gasping in type, and were interrupted frequently by paroxysms of violent, nonproductive cough. Cyanosis was very marked, and, though the atmosphere of an oxygen tent made him slightly less uncomfortable, it did not perceptibly influence his dusky color.

Fig. 2 (case 1).—Representative sections of lung. Taken from different parts of both lungs, these illustrate the extent and remarkable uniformity of infiltration. Both lungs were filled with innumerable small discrete nodules, no portion of either being spared (X 2½).

Physical examination of the chest showed tachypnea, with relative prolongation of the expiratory phase of breathing. The lungs were resonant throughout, but normal vesicular breath sounds were everywhere much reduced. Numerous fine and medium moist inspiratory and expiratory rales were present throughout both lungs; sibilant rales of the asthmatic type, also generalized, were most prominent in the expiratory phase. The heart was of normal size; heart sounds, though very rapid, were normal, and

no murmurs were heard. Examination revealed no other abnormalities. The patient was extremely weak and utterly exhausted, so that, although fully conscious, he spoke only single words, and these with considerable effort.

Laboratory studies gave the following findings. The urine was normal except for a faint trace of albumin. Blood studies showed that the hemoglobin level was 14.1 gm. per 100 cc.; the white blood cell count was 26,600, with 85% neutrophils, 13% lymphocytes, and 2% monocytes. The sedimentation rate was 77 mm. in one hour; the carbon dioxide-combining power was 35 mEq. per liter (79 vol. %). Blood cultures were sterile. Sputum showed gram-negative bacilli on smear and paracolon bacilli on culture, but was negative for fungi, both microscopically and on culture. During the patient's four-day hospital stay, the only significantly changing laboratory finding was a progressive rise of the blood carbon dioxide level from 35 to 45 mEq. per liter (102 vol. %). Concomitantly, the serum chloride level decreased from 87 to 82 mEq. per liter and the blood urea nitrogen level rose slightly from 17.5 to 25 mg. per 100 cc. on the day of death. Serum levels of sodium and potassium were normal. X-ray examination of the chest (fig. 1) revealed innumerable nodular densities uniformly scattered throughout the lung fields. These varied in diameter from 1 to 5 mm., and there was confluence of the lesions in the upper one-third of each lung. From a roentgenologic viewpoint, the appearance was consistent with that in miliary tuberculosis or in one of the other conditions capable of producing diffuse nodular infiltration of the lungs. An electrocardiogram on the second hospital day revealed sinus tachycardia, rather tall P waves in leads 2 and 3, and slight irregularity of rhythm due to a "wandering pacemaker."

Fig. 3 (case 1).—Cross section through bronchiole, showing lumen almost filled by partially organized fibrin plug. Remnant of lumen is crescentic in shape and is partly lined by epithelium. At upper right, muscular coat is fragmented and plug is firmly attached to the wall (X 100).

At the time of the patient's admission, the clinical picture was that of an acute and widely disseminated pulmonary infection, unlike any of the familiar varieties, together with severe pulmonary insufficiency, which appeared likely to lead rapidly to a fatal outcome. The patient was placed in an oxygen tent; he was given codeine and later meperidine (Demerol) hydrochloride for suppression of his exhausting cough. He received several intravenous doses of aminophylline, which at first seemed to reduce bronchospasm; after the first 12 hours, however, this drug was clearly ineffective. Penicillin, streptomycin, and chloramphenicol (Chloromycetin) were administered intramuscularly in full doses. After a very brief period of slight improvement, the relentless downhill course of the disease continued. Early on Oct. 1, 1955, the patient's condition became rapidly worse, and during that day he became irrational and then comatose. He died on the evening of Oct. 1, 1955, having failed to respond to digitalis, diuretics, or emergency measures. Autopsy revealed no abnormalities elsewhere than in the lungs; these weighed 800 gm. (right) and 700 gm. (left), contained a slight excess of blood and edema fluid, and were filled throughout with innumerable small, discrete, grossly palpable nodules. No portion of either lung was spared. Microscopic sections (fig. 2-5) showed these nodules to be typical lesions of bronchiolitis fibrosa obliterans. The results of complete bacteriological, mycologic, and virologic examinations of pulmonary tissue at the laboratory of the Minnesota State Board of Health were essentially negative. The heart weighed 340 gm. and was normal throughout.

Case 2.—A 31-year-old farmer, brother of the patient in case 1, inhaled irritating fumes on the same day (Sept. 1, 1955), in the same silo chute, and under the same circumstances as his brother. He immediately noted cough and weakness, was nauseated, and vomited. Thereafter he was never totally well but was not incapacitated. He coughed and wheezed intermittently and became gradually more dyspneic. Rapid progression of symptoms began about Sept. 22, 1955, and on the following day he was found to have fever. His physician was consulted on Sept. 24; the patient was hospitalized at Glencoe on Sept. 26. X-ray examination (fig. 6) showed innumerable discrete miliary nodules throughout both lungs, without confluence. His condition, already critical, became rapidly worse. On transfer to Northwestern Hospital, Minneapolis, on Sept. 27, he appeared slightly less gravely ill than his brother (case 1) but became rapidly worse and died in shock and stupor 18 hours after admission. The blood carbon dioxide level was 34.5 mEq. per liter (77 vol. %). Cultures were all negative. Bone-marrow biopsy findings were normal. Autopsy findings were closely similar to those in case 1. The right lung weighed 650 gm. and the left 550 gm.; both contained a slight excess of blood and edema fluid. Microscopic sections of the lungs revealed that they were filled with the tiny nodular lesions of bronchiolitis obliterans, identical with those found in case 1.

Fig. 4 (case 1).—Further stage in organization of a bronchial plug. About half of the muscular coat remains intact but elsewhere has been destroyed (arrows), permitting free ingrowth of fibroblastic tissue. Lumen is obliterated, and no epithelium remains (X 100).

Case 3.—A 48-year-old male farmer filled his silo with corn silage on Sept. 2 and 3, 1955. He climbed the ladder in the chute Sept. 4 and had to ascend twice because he was nearly overcome by fumes; he was forced to abandon his first attempt. After recovering from this exposure, he felt quite weak but stated that he had no cough or dyspnea until Sept. 23, when he developed shortness of breath and diarrhea. The dyspnea progressed rapidly and led his physicians to hospitalize him on Sept. 27. On admission, the patient's temperature was 100 F (37.8 C), his pulse 112 per minute, and respiratory rate 30 per minute. He became steadily worse, while receiving antibiotics and oxygen. X-ray study (fig. 7) showed diffuse nodular infiltration throughout both lungs. The nodules were larger and the infiltration appeared even more extensive than in cases 1 and 2. On Oct. 1, at the suggestion of a consultant, intramuscular administration of 10 mg. of prednisolone (Delta Cortef) three times a day was started. The response was dramatic, and the patient felt better in 12 hours. On Oct. 3, a roentgenogram showed some clearing of the pulmonary lesions. The patient was discharged on Oct. 10, 1955, and has remained well. He returned to work about Nov. 1, 1955. Serial x-ray studies of the chest (fig. 8) have shown progressive resolution of the nodules, but in March, 1956, tiny nodular densities were still detectable throughout both lung fields.

Fig. 5 (case 1).—Late stage of obliteration of a bronchiole, whose original location is marked only by two fragments of the muscular coat (arrows). These lie in the midst of proliferating fibrous connective tissue, which is also overgrowing and obliterating the architecture of surrounding lung tissue (X 100).

Case 4.—A 45-year-old male farmer began to add corn to his silo (still nearly one-half full of alfalfa silage put there in May, 1955) during the morning of Sept. 23, 1955. On Sept. 24, he climbed a ladder in the chute to look for a lost tool, noted irritating fumes and "inability to get air" about half-way up, and was forced to rest before descending. He was almost free of symptoms until Oct. 3. Dyspnea was noticeable then and increased steadily; he first visited his physician on Oct. 14. Breathing was more labored by Oct. 17, and the patient went to the hospital for x-ray study of the chest (fig. 9), which showed extensive, diffuse nodular pulmonary infiltration. He returned home, but was practically unable to move because of dyspnea. At the time of his admission to the hospital on Oct. 20, his temperature was 102.2 F (40 C) and his pulse 112 and respirations 54 per minute; cyanosis was pronounced. He immediately received prednisone in full doses and was given no antibiotic. Considerable improvement was noted within 24 hours. By Oct. 29, therapy was discontinued, and he was discharged from the hospital on that day. He had employed over-ripe corn as silage and had used heavy nitrate fertilization this year for the first time. He returned to work Nov. 20, 1955. Roentgenograms made at intervals demonstrated resolution of the nodular infiltrate, which, however, had not completely disappeared on Jan. 30, 1956 (fig. 10), although the patient had disclaimed any residual symptoms for one month previously.

Characteristics of Syndrome

The following cardinal points, noted in all four patients, can be considered characteristic of the clinical picture of silo-filler's disease with bronchiolitis obliterans. 1. There is a history of inhalation of irritating gas in or about a silo within a short time (from a few hours to three or four days) after filling is commenced. 2. Cough and dyspnea with a sensation of "choking" and severe weakness are noted immediately upon exposure and do not relent completely during the illness. 3. There is a two-to-three-week period after exposure characterized by a relative remission of symptoms, though some cough, malaise, and dyspnea remain and weakness progresses. 4. Onset of a second phase of illness occurs about three weeks after initial exposure, often accompanied by chills. There is fever, with progressively more severe dyspnea, cyanosis, and cough, which do not respond to administration of antibiotics, oxygen, or bronchodilators and lead to death (or else to the beginning of recovery) three and one-half to six weeks after exposure. 5. Numerous fine and medium moist (bubbling) inspiratory rales are heard over the entire extent of both lungs, together with a few moist expiratory rales and prominence of sibilant,

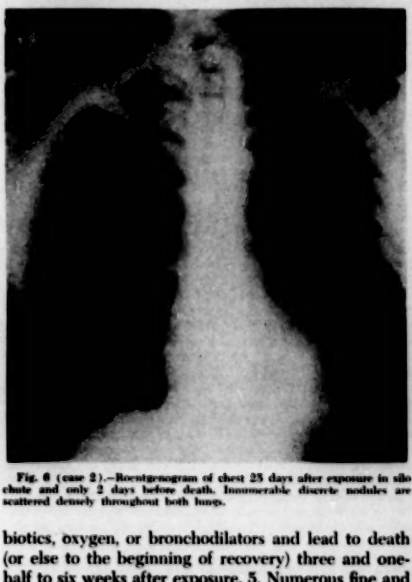

Fig. 6 (case 2).—Roentgenogram of chest 25 days after exposure in silo chute and only 2 days before death. Innumerable discrete nodules are scattered densely throughout both lungs.

asthmatic-type rales during expiration (signifying obstruction of small bronchi and bronchioles). 6. X-ray examination of the chest reveals uniform infiltration of all lung tissue with innumerable discrete nodular densities. The typical roentgenogram cannot be distinguished from that in acute miliary tuberculosis (or

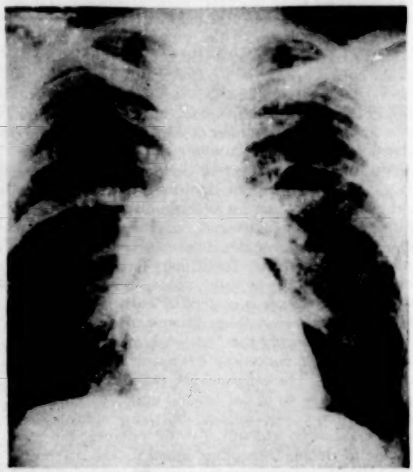

Fig. 7 (case 3).—Chest roentgenogram 23 days after exposure to silage fumes.

any one of the other conditions producing diffuse miliary nodulation in the lungs). Confluence of the lesions may be found in severe and advanced cases (e. g., case 1). 7. Laboratory studies show moderate to

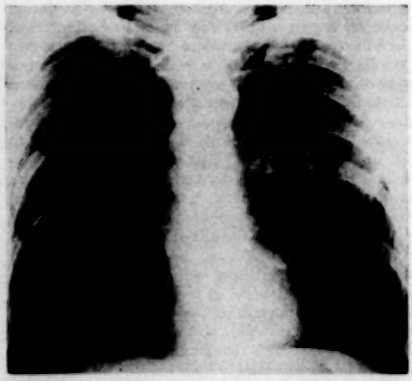

Fig. 8 (case 3).—Roentgenogram made 24 days after that in fig. 7 and 20 days after start of treatment with hydrocortisone and prednisone.

marked neutrophilic leukocytosis. In the late stages of the disease, progressive increase of blood carbon dioxide levels, indicating retention of this gas in spite of extreme respiratory effort, is, in our experience, a poor prognostic sign. Results of all other laboratory tests are normal; cultures of blood, sputum, and bone marrow for bacteria and fungi and virus studies are all negative.

Etiology and Pathogenesis

The diseases that occurred in these four individuals are seen to have been remarkably similar in pattern; the similarity of roentgenographic findings is equally striking, since the picture is an unusual and distinctive one. Our working hypothesis, at this point, formulated for the purpose of eventual testing, is that all four patients were afflicted with an apparently identical illness produced by one and the same etiological agent. On that assumption, all four cases are instances of bronchiolitis fibrosa obliterans, since this diagnosis has been proved by autopsy for the patients in cases 1 and 2. Moreover, since no significant pathogen has

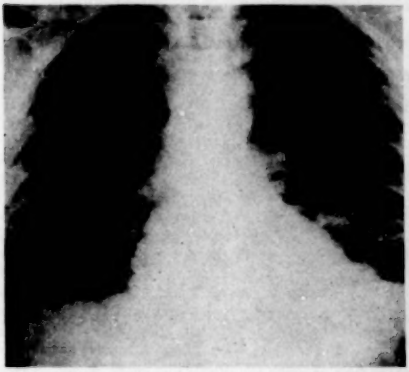

Fig. 9 (case 4).—Chest roentgenogram 23 days after exposure to silage fumes and 3 days prior to administration of first dose of hydrocortisone.

been recovered by culture from any of the patients, the initial inhalation of irritant gas by all of them must tentatively be considered the most likely cause of the illness.

The next essential step in developing the above hypothesis is identification of a gas that is (1) irritating to the surface lining of the respiratory tract, (2) capable, on inhalation, of causing bronchiolitis obliterans in man, (3) demonstrated to be formed early in the course of silage fermentation, and (4) evolved by silage, under conditions that may occur in normal silo operation, in concentrations sufficient to cause pulmonary disease (including bronchiolitis) in man and animals.

Incidence and Pathogenesis of Bronchiolitis Obliterans and the Possibility of Causation by Nitrogen Dioxide.—The pathological entity, bronchiolitis obliterans, is indeed rare. In a series of 70,281 autopsies performed during the 34-year period from 1919 to 1952, filed and indexed in the department of pathology, University of Minnesota Medical School, there were noted but two instances of bronchiolitis oblit-

erans. The pathological features of the condition are very distinctive, and rigid criteria must be employed in making this diagnosis. The lungs contain innumerable, uniformly distributed lesions, which are grossly visible and palpable as firm, discrete nodules of miliary size. Microscopically, each nodule consists of a small bronchus or bronchiole filled with a rather cellular fibrinous exudate; organization of this adherent plug of fibrin by ingrowth of fibroblasts from the bronchial walls tends eventually to occlude the lumen. Bronchiolitis obliterans can be caused by inhalation of an irritant gas[4] or can occur as a complication of certain infections[5] of the lungs and bronchi. It can also be of unknown etiology. Of the known causes, gas inhalation is the most frequent and the most definitely identifiable. It has been shown clinically and experimentally that the oxides of nitrogen[6] as well as certain other toxic gases[7] are capable of producing the condition. These others include phosgene, chlorine, chloropicrin, ammonia, hydrogen chloride, and probably sulfur dioxide. Statistically, the oxides of nitrogen—ordinarily nitrogen dioxide and tetroxide,

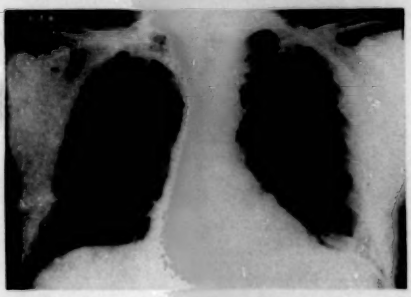

Fig. 10 (case 4).—Appearance of chest on follow-up visit three months after discharge. Patient clinically well.

both of which are relatively stable—have been incriminated in a majority of the total documented cases of bronchiolitis obliterans caused by irritant gas.[8]

Among the first gases to be considered, then, in our search for a toxic agent that might cause silo-filler's disease, were the oxides of nitrogen. At that point in the investigation, our attention was directed to a recent review by McAdams[9] in which one fatal case of bronchiolitis obliterans due to accidental nitrogen dioxide inhalation was reported. The circumstances of exposure in his case—explosion of several flasks containing red fuming nitric acid in a laboratory, which quickly filled with dense fumes of nitrogen dioxide—identified the gas beyond doubt. The clinical course of the victim's illness—even as to duration of each of its phases—and the observations made at autopsy were identical with the corresponding features in our cases 1 and 2.

Production of Nitrogen Dioxide in Silos.—In the agricultural literature and that of veterinary medicine, reports have been found[9] that contain acceptable evidence that nitrogen dioxide, in toxic amounts, may be given off in the process of silage fermentation. We do not know, as yet, how frequently this occurs, nor will it be possible, until analyses of air samples from silos have been conducted during the 1956 growing season, to measure directly the concentration of nitrogen dioxide attained in full-scale silos. In the meantime, however, information obtained indirectly, through analyses of gas evolved by experimental miniature silos, has been most helpful.

During our studies of this entire problem of toxic "silo gas," we have frequently sought the assistance of our colleagues in the agricultural sciences. Briggs, Jezeski, and Otis,[10] already engaged in a research project concerned with many aspects of silage-making, have in operation a number of miniature experimental silos in which they are studying the properties of different crops with respect to their potential value as silage. The temperature, moisture, nitrate content, and other factors can be altered and accurately controlled in this apparatus, and the gaseous products of silage fermentation under different conditions can be collected and analyzed. Preliminary data derived from such experiments indicate that, although actual amounts of gas vary considerably with growing conditions, a surprisingly large amount of nitrogen dioxide is formed during the first week of silage fermentation. Observed concentrations have ranged from 200 to 4,000 ppm. These figures are not directly comparable with those to be anticipated upon analysis of air samples from full-scale silos, but they indicate that silage may, without doubt, give off sufficient nitrogen dioxide to endanger men and animals. The maximum concentration of this gas in inspired air considered safe for man is 10 to 25 ppm by volume, in contrast to the far larger amounts found in the experiments mentioned above. Peterson and co-workers,[9] in 1949, found 151 ppm of this gas in a sample of silo-room air collected two days after completion of silo filling. This is the only report we have found dealing with quantitative analysis of silo air for nitrogen dioxide. Evolution of the gas begins within a few hours after the start of silo filling, reaches a maximum between one and two days later, and continues at a decreasing rate for a week or longer. No other irritant gas has thus far been noted, and there is no reasonable likelihood that any other such gas could be produced by silage in concentrations approaching toxicity for man.[10]

It may also be stated[10] that oxides of nitrogen emanating from silage are derived almost entirely from inorganic nitrates in the plant. Thus the potential concentration of gas is roughly proportional to the nitrate concentration of the silage crop. Factors known to increase plant nitrates are drought, highly nitrated soil (such as that fertilized with nitrates), and immaturity of the plant itself.[10] A trend in modern farming methods toward increasing use of organic nitrates in fertilizing mixtures and also of other commercial chemical compounds containing nitrogen appears likely to favor increasingly high nitrate concentrations in crops generally.

Other Effects of Nitrogen Dioxide upon Lungs and Bronchi.—This discussion of silo-filler's disease would be incomplete without a brief consideration of other types and degrees of damage to the respiratory system

that have been shown, either clinically or experimentally, to result from inhalation of nitrogen dioxide, whether generated in a silo or elsewhere. As might be anticipated, most of the reports concerning nitrogen dioxide poisoning have dealt only with fatal cases, and of these a good number have been recorded. The excellent review of this subject published by von Oettingen[10] in 1941 refers to at least 175 documented fatalities due to inhalation of this gas prior to that date. The victims died of acute pulmonary edema for the most part, and survived a very short time, varying from one hour or less to a maximum of about three days, after exposure. Another smaller, but distinct, group of individuals, after inhaling toxic amounts of nitrogen dioxide, are reported to have died from bronchiolitis obliterans; these deaths have occurred about three to five weeks after exposure to the gas.

Finally, it is reasonable to suppose that inhalation of nitrogen dioxide in an amount less than that necessary to cause death may produce some degree of injury to the bronchial or bronchiolar mucosa.[11] Individuals exposed to such sublethal concentrations presumably survive the experience; they may develop minor symptoms or none at all.[12] Further careful clinical study of such survivors, both human (when discovered) and also among experimental animals, will be needed to complete the picture of silo-filler's disease. We believe that the evidence, though still fragmentary, strongly suggests that a continuous spectrum, consisting of different types and degrees of bronchopulmonary injury by nitrogen dioxide, exists, and will come to be better understood. In such a spectrum, the bronchiolitis obliterans that we have noted would occupy a place among the more severe types of nitrogen dioxide poisoning resulting from silage fumes.

With this hypothesis in mind, it is of great interest to note that two additional cases of silo-fillers disease have recently been studied by Delaney and co-workers at the Mayo Clinic.[13] One of these patients died of acute pulmonary edema 36 hours after exposure to fumes in a silo that he was in the process of filling. The second patient also inhaled fumes inside a silo that was being filled; he developed a protracted chronic illness, with extensive bilateral pulmonary infiltration. However, he was never gravely ill, and, although the appearance of the chest roentgenogram closely resembled that seen in bronchiolitis, the clinical course was far different, since this man recovered spontaneously after six to eight weeks of illness without receiving one of the corticosteroids or related compounds. It is our impression that this man had an extensive, confluent bronchopneumonia rather than a true obliterating bronchiolitis.

These cases, reported by Delaney and associates, serve to reinforce the suggestion that in silo-filler's disease we are dealing with a continuous spectrum of conditions whose manifestations are likely to differ widely and whose degree of severity depends upon (1) concentration of nitrogen dioxide inhaled and (2) duration of exposure in each individual instance. Clearly, the conditions of exposure may vary greatly, and the only essential clinical feature common to all cases is a definite history of recent inhalation of irritating fumes (nitrogen dioxide) in or near a silo.

At the present time, then, we may state that nitrogen dioxide poisoning can occur as a result of inhalation of fumes given off by fresh silage. Silo-filler's disease seems to us an appropriate and descriptive name for cases of respiratory disease clearly shown to have resulted from inhalation of nitrogen dioxide in this fashion.

Experimental work is planned that ultimately should define much more clearly the safe limit of concentration for nitrogen dioxide in inspired air. Other studies now in progress are designed to determine accurately how much time must elapse after silo filling begins before a dangerous quantity of nitrogen dioxide may accumulate; at the same time, the maximum duration of a dangerous period in silos will be determined. Finally, a simple qualitative test for nitrogen dioxide should be developed. Such a test, to be practical, must be reliable, so that the farmer who employs it may know when he can safely enter his filled silo. Furthermore, it must be sufficiently simple and rapid so that he will not be unduly delayed in his daily activities.

Prevention

Prevention of the inhalation of silo gas is simple, in theory at least. At the present time, a reasonable plan that may be suggested to farmers is as follows: 1. Allow no one to enter a silo for any purpose from the time filling begins until 7 to 10 days after it is finished. 2. Provide good ventilation about the base of the silo during this period, so that toxic gases, if they develop, will be carried away. 3. Provide fencing (or other effective means) to prevent children and animals from straying into any spaces adjoining a silo during this dangerous period. 4. Always run the blower fan before entering any silo.

The first of these rules alone, if strictly followed, would effectively prevent silo-filler's disease in man. The difficulty remains, however, that farmers generally have known for a long time that silos are dangerous during the week immediately after filling, but their actions do not reflect this knowledge. Each of the four patients in this series stated that he knew he was taking a risk when entering a recently filled silo. The fact that not one of them was deterred by the knowledge strongly suggests that their ideas about this "possible" hazard were not sufficiently definite to make them regard the danger as real. It is hoped that the concrete information embodied in this report may, by better defining the hazard, cause it to be regarded more realistically. It will be well to reemphasize here a point that is now self-evident. By outlining for farmers and silo workers the limits of a danger that they have long recognized as existing in a vague manner, we can show them how to eliminate this hazard from silo operation. Clearly, this simple means of increasing the safety of silos cannot possibly be considered as a deterrent to the making of silage. On the contrary, it should be regarded as justification for an even wider use of silage and of silos, with a serious, if limited, hazard eliminated.

Treatment

Since exposure to the higher concentrations of silo gas or nitrogen dioxide must be rapidly fatal in spite of any treatment, prevention is obviously the treatment of choice. Up to the present time, there has been very little experience with treatment of those who survive the immediate postexposure period. Although further extension and proof are required, it is deemed worthwhile to mention the apparently favorable response to corticosteroids noted in two patients (cases 3 and 4).

It may reasonably be inferred, from the cases reported here, that, if an individual inhales a toxic amount of nitrogen dioxide, diffuse nodular infiltration of the lungs is one of the likely consequences. The histories of the patients in cases 3 and 4 strongly suggest that any patient developing bronchiolitis obliterans of this type should receive full doses of hydrocortisone, prednisone, or one of the related steroids as promptly as possible. However, the diagnosis must be assured before these drugs are used, because several widespread infections, particularly miliary tuberculosis, may create a similar x-ray picture (and sometimes clinical picture as well); in such conditions, the use of steroids alone is not the most desirable form of treatment. The fact must be emphasized that this diagnosis requires an undoubted history of inhalation of irritating gas or fumes in or near a recently filled silo.

Summary and Conclusions

A newly recognized clinical entity, namely, bronchiolitis fibrosa obliterans caused by inhalation of oxides of nitrogen produced in recently filled silos, was seen in four patients. The facts leading to our conclusion regarding etiology were as follows: 1. All four patients became ill immediately upon inhaling irritating fumes in a silo or silo chute, and exposure occurred within 48 hours after filling of the silo was initiated. 2. All four presented clinical and roentgenographic findings of bronchiolitis obliterans. Two of the patients died and were found, at autopsy, to have the classic pathological lesions of the condition. 3. Nitrogen dioxide is an irritant gas and has been demonstrated to be capable of causing bronchiolitis obliterans upon inhalation. No other gas fulfilling these criteria has been found to emanate from silage. 4. Experimentally, nitrogen dioxide is shown to be produced early in silage fermentation; under certain conditions of soil and moisture, high concentrations—far higher than the safe limit for man—occur. We have chosen to designate as silo-filler's disease the group of pathological and clinical entities resulting from the inhalation of nitrogen dioxide in or near freshly filled silos; bronchiolitis obliterans arising from this should be regarded as one form of silo-filler's disease. Nitrogen dioxide inhalation may (in theory at least) produce a variety of bronchopulmonary conditions; the chief factor determining the type of damage is the amount of the gas inhaled. A recent report of two instances of silo-filler's disease that were widely different from our cases tends to support this conclusion. It is noted that the present trend in agriculture toward greater use of commercial chemicals containing nitrogen may tend to increase production of nitrogen dioxide from silage and hence may increase the possibility of exposure to this gas. Safety measures will prevent the inhalation of toxic silo gas, provided they are enforced. Two cases of bronchiolitis obliterans have been treated with adrenocortical steroids, with apparent success. It is important to establish a firm diagnosis (based essentially upon history of exposure) before using one of these drugs.

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Drs. Duane C. Olson and V. A. Schulberg, Gaylord, Minn., gave permission to report case 3. Drs. H. G. Deerhake, P. A. Connaughton, and E. Steere, Lima, Ohio, gave permission to report case 4.

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Lung Abcess.—In all the annals of medical therapeutics, one cannot find a story to parallel the progress made in the treatment of pulmonary abscesses. A scant 18 years ago saw pulmonary abscesses carrying a mortality of 34 per cent and a morbidity even higher than that. If a patient were fortunate enough to survive the acute phase of his abscess, in approximately 50 per cent of the cases, he would carry a chronic draining broncho-pleural cutaneous fistula, bronchiectasis, or recurrent pulmonary hemorrhage, which would eventually cause his death. Recently Waterman and Dorm showed that the mortality rate in over 200 cases was less than 10 per cent. Even more important is the lowering of the morbidity following an acute pulmonary abscess. With the use of antibiotics, conservative draining procedures, and surgery, one is able to handle satisfactorily 80 per cent of the acute lung abscesses. The major contributing factor in this miraculous change in a very serious disease is the antibiotics that are now available for the treatment of acute pulmonary infections. In addition to this, the improved techniques for thoracic surgery have lowered the mortality and morbidity of those cases not responding to ordinary therapeutic measures. In spite of this very optimistic picture, we feel that lung abscesses still must be considered a serious disease.—W. A. Hopkins, M.D., J. Free, M.D., and M. B. Davis, M.D., The Treatment of Lung Abscess, *Journal of the Medical Association of Georgia*, February, 1956.

HYPOTHYROIDISM IN THE ADOLESCENT

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• *Important criteria for judging the status of adolescent patients with respect to the thyroid are the measurement of the uptake of radioactive iodine by the thyroid, the measurement of protein-bound iodine in the plasma, the response of both measurements to administration of the thyroid-stimulating hypophysial hormone, the basal metabolic rate, the serum cholesterol level, and the skeletal age as measured by hand-wrist roentgenograms. In one case here described, inadequate treatment of congenital cretinism had resulted, by the age of 13 years, in physical, emotional, and intellectual retardation; in a second case, myxedema resulted in pseudo-obesity and retarded skeletal growth; in a third, the skeletal age was two years less than the chronological age of 17 years, and sexual maturation had barely begun. Medication with desiccated thyroid had strikingly beneficial effects in these three. A fourth patient appeared to be overweight and had a low basal metabolic rate by surface-area standards; by height standards, however, his basal metabolic rate was found to be normal. Other criteria also showed that his thyroid status was normal. On suitable dietary management alone the changes of adolescence in this patient were completed normally without thyroid.*

Certain misconceptions regarding hypothyroidism in the adolescent are encountered so frequently that it would appear profitable to review some of the clinical and laboratory aspects of this disorder. Too often the obese adolescent is thought to be hypothyroid when actually there is no clinical or laboratory evidence to support the diagnosis. In contrast, the cold-skinned, thin, slow-maturing adolescent is rarely considered a thyroid problem, and yet a thorough diagnostic study may reveal him to have a thyroid deficiency. Furthermore, inaccuracies in computing the basal metabolic rate in the obese patient who complains of fatigue are common enough to merit further discussion. Such matters and representative cases of hypothyroidism in the adolescent are presented in this review.

Hypothyroidism in the adolescent differs from that in the adult in one important aspect. This difference is its effect on growth and development. The progress of osseous growth and development is dependent in part on adequate levels of thyroid hormone, and prolonged thyroid deficiency that retards osseous development in the growing child or adolescent obviously cannot affect in this way the adult whose growth is complete. Clinically what one sees is a retardation or a cessation of growth in a child whose growth had previously been progressing in an orderly fashion. These findings alone do not make the diagnosis of hypothyroidism but should alert the physician to a careful and thoughtful appraisal of the adolescent's growth and development.

While clinical evaluation remains the most important factor in the diagnosis of thyroid dysfunction, a number of laboratory aids have proved their usefulness. These can be classified either into measurements of thyroid hormone synthesis or into measurements of metabolic defects resulting from alterations in the levels of circulating thyroid hormone. We include in the former the measurement of the uptake of radioactive iodine (I^{131}) by the thyroid gland, the measurement of protein-bound iodine in plasma, and the response of both these indexes to the thyroid-stimulating hormone of the pituitary. Among the changes that are secondary to the decrease in circulating thyroid hormone, we measure basal metabolic rate, serum cholesterol level, and bone age.

The determination of the basal metabolic rate merits some discussion. The basal metabolic rate is still to be considered a useful measurement, but its many limitations have to be kept in mind when interpreting the results. It is not a direct measure of thyroid function but a measure of the resting metabolic state. Technical errors are frequent but relatively easy to detect: endogenous interferences resulting in failure to obtain a true basal metabolic level can usually be established by careful questioning and observation of the patient. The chief and least frequently recognized error arises in the calculation of the metabolic rate of obese adolescents.

That formulas that include weight produce erroneous results in those patients is easily understood when one realizes that up to 30% or more of total body weight may consist of fat, which we know to have a low metabolic activity. In fact, basal metabolism seems to be closely related to fat-free active tissue mass.[1] If this is the case, this, rather than a formula that includes total weight, would be a more accurate basis for determining basal metabolism. Unfortunately, however, at the present time the measurement of fat-free tissue is impractical for routine use.

When the patient's fat is not taken into consideration in the calculation of the basal metabolic rate, an erroneously low figure for basal metabolic rate will be obtained. This error is especially likely when surface area standards are used[2]; the reason for this is that as weight increases the surface area does not increase in proportion to the increase in body tissue mass.[1] In our experience it is helpful to calculate the basal metabolic rate of overweight adolescents on the basis of standard height tables.[2] It is to be remembered that the basal metabolic rates calculated in this manner tend to be a little high, but they certainly cor-

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relate more closely with one's clinical impression and with other laboratory tests than do the basal metabolic rates of young obese patients calculated on surface area standards.

From the foregoing, it is clear that the basal metabolic rate of an obese adolescent should be carefully evaluated and appropriately calculated. If it is low, careful appraisal of its method of calculation and of the patient's history and physical examination should be made. Subsequently, any lingering doubts about thyroid deficiency can usually be resolved by such measurements of thyroid function as I^{131} uptake and protein-bound iodine level. As a screening method, determination of the protein-bound iodine level seems to be the most satisfactory means of assaying thyroid function.[3] This test is accurate and reproducible and represents a relatively direct measure of circulating levels of thyroid hormone. The possibility of its invalidation by previous iodine therapy should, however, be kept in mind.

The evaluation of skeletal age by means of hand-wrist roentgenograms is a valuable procedure in the study of patients presenting growth problems.[4] Lowered body metabolism due to true thyroid deficiency directly affects and retards skeletal growth, and if the bone age is equal to or advanced beyond the chronological age, there is little reason to suspect thyroid deficiency. However, retarded skeletal development may represent a normal variation in growth, may be evidence of hypothyroidism, or may accompany pathological processes other than hypothyroidism.

Report of Cases

Case 1.—A patient had congenital hypothyroidism or cretinism that had been inadequately treated over a period of many years. The most striking findings were the generalized retardation of all osseous development, poor peripheral circulation, and failure of certain body structures to differentiate. The patient came to the adolescent unit of the Children's Hospital at age 13 because of physical, emotional, and intellectual retardation. Her present illness dated from infancy. Her delivery had been normal, but in the first six months of life she was slow, sleepy, and a poor eater. Her weight gain was slow and food intake poor. When she was 17 months of age, a physician said she had an incurable glandular disease and prescribed two small white pills after each meal. This medication was continued for years, but its administration was sporadic and according to the mother's or the child's whims. The child's growth and development continued to be slow and her appetite poor until the time she was seen in our unit.

The patient's height was 43 in. (109.2 cm.) and her weight 68 lb. 12 oz. (31.1 kg.). Her blood pressure was 80/60 mm. Hg, pulse rate 60 per minute, and respiration 24 per minute. She was a very small and "obese" child, with a full face and periorbital edema. Her olive skin was extremely dry and cool throughout and her hair abundant but coarse. All but eight of her teeth were primary ones. Her thyroid was not palpable. Fat pads of moderate size above the clavicles and a hump at the back of the neck were noted. The abdomen was protuberant, and an umbilical hernia was present. There was pitting edema of the lower extremities. Hematological studies showed moderate normochromic anemia. The serum cholesterol level was 440 mg. per 100 cc. A hand-wrist x-ray demonstrated a bone age of 7 years, which was six years behind her chronological age. A gradually increased dosage of thyroid extract was prescribed. After a period of adequate therapy, the patient became euthyroid, and gradually her physical status improved.

Case 2.—This patient presents a classic picture of myxedema, the end-result of prolonged hormone deprivation. Although she appeared fat, the important fact is that she was not truly obese. Her pseudo-obesity is of the type that is often taken for true obesity and has led to the confusion of hypothyroidism with obesity. This patient was brought to our unit at age 12 years and 6 months because she had changed from a very slender child to a very fat one during the previous 12 months. Two years prior to admission she had had abdominal pain for a two-week period. Gastrointestinal roentgenograms at that time were reported as showing her small intestine "almost closed." She was given a low-residue diet at that time, but her intermittent abdominal pain persisted. Formerly a sound sleeper, she began to wake easily at night, and, although she had had a good appetite, it became poor. Her mother thought that the child's hair was becoming coarser than it used to be and said that her general activity had become increasingly sluggish. Frequent bulky stools had been noted in recent months. At her first visit, we found the patient to be a pleasant, but lethargic, plump child. She said she had noticed loss of appetite and loss of energy during the previous year.

Her weight was 102 lb. (46.3 kg.) and her height 53 in. (134.6 cm.). Her skin was dry. The thyroid was soft but not enlarged. Her abdomen was protuberant. The reflexes were sluggish but equal. Her bone age was two years less than her chronological age. She showed a mild normochromic anemia. The serum cholesterol level was 180 mg. per 100 cc., and the protein-bound iodine was below a measurable amount. The patient was considered to have acquired myxedema and was given 30 mg. of thyroid extract daily. Her most striking response to thyroid extract was the resumption of her growth. She also had an initial weight loss followed by a weight gain, and her skin and peripheral circulation changed to a normal state.

Case 3.—It is the obese adolescent whom the physician is most frequently asked to evaluate, and the basal metabolic rates should be calculated with due regard for the effect of excessive fat on the result. This patient had gained weight rapidly during his 13th year. His mother said that for the previous 12 months he had been overweight and that he was still gaining weight. She explained that she herself was taking thyroid extract. She believed that her son should have a metabolism test and that he needed thyroid extract.

On his first visit the patient was 13 years and 8 months of age. His height was 66.5 in. (168.9 cm.) and his weight 127 lb. (57.6 kg.). He seemed to be an alert, healthy, well-adjusted young boy whose appearance was typical of a moderately fat adolescent. His hair was not coarse; his eyebrows were not thin. The palms were moist, and his extremities were warm. There was nothing sluggish about his behavior, and his success in both his school work and his outside activities was good. His basal metabolic rate calculated on surface area standards was −15%, but when calculated on height standards it was −2%.

The patient appeared to be a perfectly normal young adolescent. It was suggested that he restrict himself from such fattening foods as gravy, mayonnaise, and cream and fried foods but that he continue to eat a diet relatively high in protein and calories. He was told that his growth and development were perfectly normal and that in all probability as he grew taller he would thin out, but that processes of growth and development could not be predicted with absolute certainty and that it would be well for him to be seen at three-month intervals for evaluation of his progress. It was believed that this recommendation would not only reassure the boy but also make it less likely that the mother would take him from doctor to doctor until "hormone injections" or thyroid extract were prescribed or until he would reach the point where he would be really convinced that he was abnormal. Twenty-four months later, when he was 15 years and 8 months of age, his height was 67 in. (170.2 cm.) and his weight 132 lb. (59.9 kg.). He had completely lost the chubby appearance of a boy in early adolescence and had acquired the secondary sexual characteristics of an adult male.

Case 4.—At age 17, a patient came into our unit because of headaches, easy fatigability, fainting episodes, and slow maturation. Six months prior to admission he had noticed that his appetite was poor, that sports fatigued him quickly, and that he required more sleep than usual. Three months previously he began to have weak spells and fainted on several occasions. The fact that his younger sister was 4 in. taller than he was irritated him. He was a very pleasant, responsive boy who was puzzled by his symptoms and disgruntled with his small stature. He was 60.75 in. (154.3 cm.) tall and weighed 100 lb. (45.4 kg.). His pulse rate was 60 and his blood pressure 120/80 mm. Hg. His hair was brittle and coarse, and his skin was cool and dry.

The thyroid was not palpable. Sexual maturation had barely begun. The laboratory results confirmed the clinical impression of hypothyroidism. The bone age was two years less than his chronological age of 17 years. The serum cholesterol level was 245 mg. per 100 cc., the protein-bound iodine level was 2.4 mcg. per 100 cc., and the basal metabolic rate was –33%.

Administration of desiccated thyroid extract was begun, and the amount given was gradually increased. His easy fatigability diminished, and his alertness and responsiveness and appetite increased. His growth progressed, and his skin became warm and was not dry. In our experience this form of hypothyroidism is often unrecognized. It was not clear whether this boy had acquired hypothyroidism or whether he had a transient depression of thyroid function, but it is a fact that during thyroid extract therapy his physical status made a striking improvement. It should be emphasized that very few thin, late-maturing adolescents are hypothyroid, but this possibility should be kept in mind.

Comment

The first two patients illustrate situations classically associated with hypothyroidism and without essential differences in the adolescent age group. The fact that patients presenting similar findings are occasionally seen in a practice confined to the adolescent age group indicates the need to be on the lookout for adolescents whose hypothyroidism has had inadequate treatment in earlier years or who suffer from classic myxedema.

The third and fourth case reports illustrate the situations encountered when hypothyroidism is considered in the differential diagnosis of the obese or slow-maturing adolescent. The opinion that a fat, sluggish, fatigued adolescent who has a low basal metabolic rate has hypothyroidism still persists. However, when these young people are more carefully studied, little is found to suggest that thyroid deficiency exists. The history obtained from these obese adolescents is that of gradual accumulation of subcutaneous fat. Frequently this is associated with complaints of sluggishness or fatigue. The dietary history is invariably one of a normal to prodigious appetite, never an impaired one. A normal to prodigious appetite is incompatible with the diagnosis of true thyroid deficiency. Furthermore, the growth of these young persons, as determined by history, physical examination, or bone age, is normal. This militates against thyroid deficiency, since retarded growth is one of the outstanding features of hypothyroidism in adolescence. The physical examination also fails to divulge any of the classic features of hypothyroidism. The skin is warm, the palms are moist, the complexion is ruddy, the hair is not coarse, and there is no thinning of the outer eyebrows. Pulse rate and pulse pressure are found to be in the normal range, and subcutaneous tissue is firm in contrast to the loose, thick turgid skin seen in myxedema.

Case 3 illustrates the need to keep in mind that many young people tend to put on subcutaneous fat during early adolescence and that this in itself is not suggestive of hypothyroidism. In particular, great care should be used in interpreting basal metabolic rates in these patients. Desiccated thyroid extract should never be given on the basis of a single low metabolic rate; a low determination should only provoke a more critical evaluation of the entire clinical picture. Further laboratory investigation may be indicated if reappraisal still leaves the question of hypothyroidism in doubt.

On the other hand, a thin, dry and cold skinned, irritable adolescent (case 4) is often not given the benefit of a therapeutic trial with thyroid extract because the presence of hypothyroidism is not suspected. The majority of thin, late-maturing patients will be found to represent only normal variations in growth and development, but a small percentage will be found to have such findings and signs as slow growth, poor appetite, intolerance to cold, short stature with minimal subcutaneous tissue, cold, dry skin and dry palms, retarded sexual maturation, thin eyebrows, a bone age two to three years behind chronological age, a low protein-bound iodine level, and an elevated serum cholesterol level. This form of acquired hypothyroidism is not the classic picture as described in the literature, but various authors recognize this syndrome as a stage in the development of hypothyroidism.[5]

The primary purpose in the treatment of uncomplicated hypothyroidism is to restore the adolescent to a euthyroid state as safely and rapidly as possible. The dose must be adequate to reverse the abnormal physiological functions and to assure resumption of osseous growth. Talbot and co-workers [6] recommend a dosage of 60 to 90 mg. of desiccated thyroid (U. S. P.) per square meter of body surface. Full dosage should not be given at the onset. It is well to begin with one-quarter of the calculated full daily dose and then to increase the amount at two-week intervals, provided symptoms of overdosage do not occur. In adolescence, where maintenance of growth is important, the maximum dose of thyroid that can be tolerated without symptoms of nervousness, insomnia, diarrhea, and weight loss is the correct amount for that patient. This maximum tolerated dose makes possible the resumption of growth and the full utilization of the patient's inherent growth potential.

Summary

Certain misconceptions regarding hypothyroidism in the adolescent are frequently encountered. Features of the growth and developmental history and of dietary pattern often give the physician valuable clues for an evaluation of thyroid status. Obesity and hypothyroidism in the adolescent are often mistakenly associated. The thin, late-maturing, cold-skinned adolescent, who is at times not recognized as being hypothyroid, may often be so.

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UROLOGIC PROBLEMS IN POSTPOLIOMYELITIC PATIENTS IN RESPIRATORS

WITH SPECIAL EMPHASIS ON MAJOR UROLOGY SURGERY

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• *Urinary calculi occurring in postpoliomyelitic patients in respirators present important problems of prevention and treatment. No dependable methods of prevention have been developed; methods of treatment may be classified as either conservative or surgical. The possibilities of conservative treatment are illustrated in the case of a 9-year-old girl with bilateral obstruction by ureteral calculi; after cystoscopy and bilateral ureteral catheterization, the calculi passed down the ureters over a period of three weeks and were eventually passed by the urethra with minimal symptoms. Details are given of two other cases in which surgical treatment became necessary. Major urologic surgery in the renal fossa was performed successfully seven times in five patients. The lateral nephrectomy position was used; it was formerly thought that these patients would not tolerate this position. Resection of the 12th rib facilitated the approach to the kidney. Since much of the patient's muscle is replaced by fibrous tissue, dissection may be hard and hemostasis requires special attention. The use of the endotracheal tube during anesthesia, of special forms of respirators, of induction with thiopental given intravenously, of antibiotics, and of the nasogastric tube to prevent gastric dilatation, all contributed to the success of the surgery, which these patients tolerated surprisingly well.*

In the past decade, the advances made in the rehabilitation of postpoliomyelitic patients in respirators have markedly changed the prognosis for such patients. Where these people were formerly confined for life in the "iron lung," today, with the advent of new knowledge concerning pulmonary physiology, respiration techniques, chest respirators, and rocking beds, many of these unfortunate victims of poliomyelitis can be returned to a more nearly normal life. In view of these advances, it is well to reconsider the urologic aspects of their disease and, if possible, to attempt to keep abreast of the ground gained in the other fields of rehabilitation.

The primary urologic problem is urinary tract calculus formation, probably secondary to hypercalciuria, which is directly proportional to the extent of residual paralysis.[1] Most calculi consist of calcium in various combinations with phosphate, ammonia, carbonate, and magnesium. It is well to note that neurogenic bladder dysfunction is not present in the type of patient under discussion, except for temporary bladder atonicity during the acute phase of the illness. The problem may be divided into two major phases: (1) the prevention of calculi by medical means, and (2) the management of calculi already present. The former has been aimed mainly at the reduction of hypercalciuria. Among the various methods may be mentioned (1) postural renal drainage,[2] (2) mobilization of the patient by rocking beds and tilt boards, (3) hormonal therapy with testosterone alone or in combination with estrogen,[3] (4) high fluid intake, (5) low-calcium diet, (6) Shorr regimen (administration of basic aluminum carbonate [Basaljel] or aluminum hydrochloride [Amphojel] to diminish intestinal absorption of phosphate), (7) parenteral administration of hyaluronidase to increase the amount of protective colloids in the urine,[4] (8) local instillation of G (Suby's) solution in an attempt to dissolve calculi,[5] (9) acidification of the urine with ammonium chloride and other acidifying drugs, (10) administration of antibiotics for control of urinary tract infection, and, most recently, (11) the use of orally given salicylates to increase urinary glucuronides.[6] To date, all of these procedures, with the exception of salicylate therapy, which as yet has not had adequate clinical trial, have proved disappointing in the prevention of new or recurrent calculus formation.

The second phase of the problem, the management of stones already present, may be further subdivided under two headings: (1) conservative therapy and (2) surgical therapy. The conservative approach to the treatment of calculi, which would include watchful waiting, cystoscopic procedures, forcing of fluids, and use of antispasmodics such as propantheline (Pro-Banthine) bromide, is obviously the treatment of choice in such cases. In considering the usual indications for cystoscopy and ureteral catheterization for drainage, one must take into account the important fact that even large ureteral calculi will pass spontaneously with unusual ease in these patients. However, as in the usual urologic practice, there are cases where conservative therapy fails and we must resort to surgery in order to preserve kidneys and even lives. In the past, any major surgical procedure, and, in particular, renal surgery, was frequently avoided because of the supposedly prohibitive operative risk and poor survival rate in patients confined to the "iron lung."[7] Recently, in view of the progress in rehabilitation of these patients and the improved techniques in anesthesiology and pulmonary physiology, it was deemed advisable to reevaluate the operative risk in patients in respirators. Employing the usual indications for operative interference and working closely with the pulmonary physiologist and anesthetist, we performed major urologic surgery seven times in five patients.

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At the time of writing, there are 28 paralyzed postpoliomyelitic patients at the New York Regional Respirator and Rehabilitation Center at Goldwater Memorial Hospital in New York City. All were confined to respirators on admission, and nearly all had had their disease for more than one year. Involvement in all cases is high spinal; no patient has bulbar involvement. Many, through rehabilitation, are able to use rocking beds and wheel chairs. All 28 patients have hypercalciuria, with a constant 2+ to 4+ reaction to the Sulkowitch test. Ten (35%) have had urinary tract calculi, two of which were of the staghorn type. All patients with calculi had significant pyuria and varying degrees of hematuria. Five patients underwent seven major urologic procedures in the year prior to writing. Two patients had bilateral renal surgery. Two had had drainage by a ureteral catheter. The remainder had purely conservative treatment.

Report of Cases

Case 1.—A 9-year-old female developed poliomyelitis in October, 1954. On admission to the center, she had pyuria, alkaline urine with a specific gravity of 1.008, and a 2+ reaction to the Sulkowitch test. A roentgenogram of the abdomen was negative for calculi. In December, 1955, the patient developed bilateral flank pain, a temperature of 105 F (40.6 C), and shock. A blood culture was positive for Proteus vulgaris. The blood urea nitrogen level, which previously had been normal, rose to 36.5 mg. per 100 cc. A roentgenogram showed bilateral midureteral calculi, one to each side, both quite large, measuring roughly 1 by 0.5 by 0.5 cm. Cystoscopy and bilateral ureteral catheterization were done without anesthetization. A cloudy drip appeared from both sides. Catheters were left in situ for drainage. Because of shock and the grave condition of the patient, surgery was deferred. The patient was placed in a respirator tank, and antibiotics were given. In two days, the temperature was normal and the blood urea nitrogen level was down to 15 mg. per 100 cc. A roentgenogram showed catheters in situ and both stones back in the renal pelves. After two days the catheters were removed. Subsequent roentgenograms showed that the calculi passed down the ureters over a period of three weeks. They were eventually passed by the urethra, with minimal symptoms.

This case demonstrates how much can be accomplished by conservative therapy, as by simple catheter drainage of kidneys. It also demonstrates that unusually large stones can pass spontaneously in postpoliomyelitic patients. It is interesting to note that, although this patient was placed on continuous salicylate therapy immediately after the acute episode, she has since developed new caliceal calcifications bilaterally. The patient has been asymptomatic since passage of the ureteral stones.

Case 2.—A 38-year-old male developed poliomyelitis in November, 1949, with resultant quadriplegia. He has been confined to a tank respirator since onset of illness. In 1952, x-ray examination of his abdomen showed multiple bilateral renal calculi. In July, 1954, the patient developed bilateral back pain, fever, pyuria, and a blood urea nitrogen level of 28 mg. per 100 cc. He was treated successfully with oxytetracycline (Terramycin). When he was admitted to the center in January, 1955, urinalysis showed that his urine had a specific gravity of 1.002 to 1.010; he had pyuria, a 3+ reaction to the Sulkowitch test, and occasional hematuria. In July, 1955, he developed tenderness of the left costovertebral angle, oliguria, and hematuria. An intravenous urogram showed multiple calculi in an atrophic, nonfunctioning right kidney and also two large calculi in the upper ureter on the left and several smaller stones in a hydronephrotic left renal pelvis. Phenolsulfonphthalein excretion was 20% in one hour. The blood urea nitrogen level was 15 mg. per 100 cc. The white blood cell count gradually rose, and the patient began to run a low-grade fever. The blood urea nitrogen level increased to 19.5 mg. per 100 cc., and the patient began to show signs of early uremia. In October, 1955, with the patient in the lateral nephrectomy position and under endotracheal anesthesia, the left kidney was exposed through the usual loin incision after resection of the 12th rib. The ureteral stones were removed through a high ureterotomy incision. A large stone was removed from an intrarenal pelvis by the insertion of a Randall stone forceps[6] via the ureterotomy incision. Six smaller stones were recovered after forceful irrigation of the calices with an antrum-irrigating nozzle. A film taken postoperatively showed no calculi remaining in the left renal area. Immediately postoperatively, the patient was placed in a tank respirator. His postoperative course was uneventful save for acute gastric dilatation on the third day, which was easily controlled with suction via a nasogastric tube. The blood urea nitrogen level on the fifth postoperative day was 11.5 mg. per 100 cc. Extensive ecchymosis was noted in the skin, but the wound healed promptly by primary intention. The calculi consisted of calcium and magnesium phosphate. There has been no recurrence of stones on the left side up the time of writing.

This case demonstrates several important points concerning the surgical treatment of patients dependent on respirators. First, it is seen that these patients can be successfully operated on. Second, the lateral position is surprisingly well tolerated by these patients when they are under endotracheal anesthesia. Because of the paralysis of the thoracic muscles, the ribs take a more vertical direction, and in order to enter the renal fossa it was found necessary to resect the 12th rib in all patients in whom the renal fossa was entered. The complication of gastric dilatation is a very real and very frequent danger in patients confined to respirators and is, in fact, a not uncommon cause of death in these patients.[7] Fortunately, prompt recognition and treatment by nasogastric suction relieve this often distressing complication. The presence of a trained anesthetist during surgery and of a trained respirator team during the postoperative period is mandatory for successful completion of surgical treatment. This patient is now employed full time by a national foundation in his capacity as a lawyer. In short, removal of the calculi and reversal of uremia have returned him to a useful existence.

Case 3.—A 26-year-old female contracted poliomyelitis in August, 1953. Because of respiratory paralysis, tracheotomy was performed and she was then placed in a tank respirator. Studies at another hospital revealed quadriplegia and a moderate hypertension. Study of the urine showed 2+ albumin, pyuria, hematuria, and a positive culture for P. vulgaris. An intravenous pyelogram showed a nonfunctioning right kidney, two calculi in the lower right ureter, and several stones of fairly large size in the left renal pelvis. Cystoscopy was done repeatedly for removal of bladder calculi apparently passed from the left kidney. Ureteral catheters passed beyond stones in the right ureter obtained no urine. In July, 1955, the patient was transferred to this center for further rehabilitation. Her condition improved to the point where she could use the chest respirator and for short periods could be placed in the rocking bed. However, in September, 1955, the patient developed pain in the left flank, hematuria, and fever. An intravenous pyelogram showed a nonfunctioning right kidney with two lower right ureteral calculi, as noted before. On the left there were several large pelvic stones and one smaller stone in the midureter. Ureteral catheters were passed to both kidneys; no urine appeared on the right, and a clear drip was noted from the left. Within a week, the stone in the left ureter passed spontaneously. We felt that, with several calculi on the left poised as potential ureteral obstructions, every attempt should be made to restore the function of the right kidney. A trial of ureteral catheter drainage from the right kidney produced only 10 cc. in 24 hours. A retrograde pyelogram showed moderate hydronephrosis.

It was decided that, in spite of poor return of urine, the risk was justified in an attempt to restore function by removal of the calculi. It would also reveal to us whether or not a kidney totally blocked for a year could function again after removal of the obstruction. In November, 1955, therefore, a right low ureterolithotomy was done through a Gibson incision,[8] with the patient under endotracheal anesthesia. The ureter was markedly bound down with a periureteral scar, and the stones were removed after considerable and difficult dissection during which several tears were made in the peritoneum. A no. 10 red rubber catheter was passed retrograde to the kidney through the ureterotomy, and frank heavy pus was evacuated. In view of the pyonephrosis and the danger of leakage of pus into the peritoneal cavity, the decision was made at the operating table to remove the kidney. The patient was placed in the lateral nephrectomy position, and, through the usual loin incision, with resection of the 12th rib, a rather difficult subcapsular nephrectomy was performed. The patient made an uneventful surgical recovery, both wounds being healed within one week. The patient did well until April, 1956, at which time she developed costovertebral pain on the left, fever, and a rise of blood urea nitrogen level to 31 mg. per 100 cc. A roentgenogram revealed a large calculus in the upper left ureter and another in the lower calix. A no. 6 ureteral catheter passed easily into the left pelvis, from which approximately 50 cc. of very thick purulent material was aspirated. The catheter was left in situ and irrigated every four hours with 15 cc. of streptokinase-streptodornase solution. The urine was nearly clear within 24 hours, and the blood urea nitrogen level returned to normal. Four days later a routine high ureterolithotomy was done through a loin incision, with the patient in the lateral position. The stone in the lower calix was obtained by flushing of the lower calix with an antral irrigator inserted through the ureteral incision. The stone was dislodged into the pelvis and easily removed with a stone forceps. The patient made an uneventful recovery.

This case illustrates two important factors. If the patient had had earlier removal of the low-lying calculi in the right ureter, kidney function might well have been preserved on that side. As it was, the delay of over a year eventually led to complete loss of right kidney function. It is further demonstrated that this type of patient can be subjected to rather extensive surgery and yet do surprisingly well. The use of the antral irrigator has proved to be a great time-saving device on several occasions. By this maneuver we have dislodged many caliceal calculi without extensive probing or nephrotomy, which is not the most desirable procedure in the case of a unilateral kidney.

The remaining three patients had four major procedures; one had a pyelolithotomy and later a nephrolithotomy on the opposite side, and the other two each had a pyelolithotomy. All operations were done with the patient under endotracheal anesthesia and in the lateral position, with resection of the 12th rib done as a necessary adjunct to good exposure. All did well during surgery and all went on to full surgical recovery.

Comment

It is not within the scope of this paper to discuss in detail the problems involved in the medical approach to the prevention of calculus formation. Suffice it to say that, up until the present time, no really satisfactory method, chemical or physical, has yet been brought forward. Salicylate therapy is as yet too new for any definite statement to be made.

The practical problem at hand, then, remains the management of calculi already present and the prevention, as far as possible, of stone formation. Spontaneous passage of large ureteral calculi is a rather common occurrence in these patients. Many cases of temporary obstruction can be easily handled by ureteral catheter drainage for short periods of time. However, not infrequently surgical intervention may become necessary to effect relief, and, in view of the fact that pyonephrosis and cortical abscesses secondary to calculi are an important cause of death in this group of patients,[7] the problem is of the first magnitude. The only previous report of urologic surgery in patients in respirators that we could find was that of Brady and Wilson, in 1948.[2] At that time, they presented two instances of major urologic surgery. The first was a low ureterolithotomy through the Gibson incision, with mask anesthesia and manual artificial respiration; the wound healed in two months. The second was a nephrectomy through the anterior transperitoneal approach for calculi, again with mask anesthesia and manual artificial respiration. The anterior approach was used because the authors did not believe that the patient would tolerate the lateral nephrectomy position. This wound closed in six weeks. The seven operations herein presented were all done with the patient in the lateral position and under endotracheal anesthesia. All patients did well during and after surgery, with healing in each case by primary intention. The two great new advantages are, of course, endotracheal anesthesia, which permits controlled breathing, and antibiotics.

The specific problems encountered may be divided into three types: anesthetic, surgical, and postoperative.

Anesthetic Problems.—The induction of anesthesia depended upon the stage of rehabilitation. If the patient was in a respirator, an ingenious plastic bell was fitted over the head support, enclosing only the patient's head. Within this bell or dome, rhythmic increase and decrease of pressure was maintained to "breathe" the patient. In the meantime, an intravenous infusion was started and induction was done with thiopental (Pentothal) sodium. Once the patient was asleep, the bell was removed and an endotracheal tube inserted and attached to the gas machine. The patient was then moved to the operating table and positioned. If the patient was in a chest respirator, induction was instituted with thiopental, the endotracheal tube was inserted, the chestpiece was removed, and the patient was transferred to the operating table. For patients in rocking beds or wheel chairs, induction was accomplished with the chest respirator and thiopental.

Surgical Problems.—The major problem at surgery was bleeding, particularly while the muscles were being incised. It was noted that much of the muscle in these patients was replaced by fibrous tissue, so that the contraction of smaller blood vessels was prevented. Hemostasis is meticulous and time consuming. As expected, there was in all cases marked periureteral and perirenal scarring that on occasion made for difficult dissection.

Postoperative Problems.—Two major problems were present in the postoperative period. The first and most serious was tracheobronchial mucus formation, which could lead to atelectasis and bronchopneumonia, the commonest cause of death in patients in respirators.[7] This hazard was combated by several means. All pa-

tients were placed in tank respirators postoperatively; intermittent coughing was produced by means of a cough machine, deep breathing was performed by the respirator, tracheal suction was done as necessary, and humidification was accomplished if indicated. The second danger lay in acute gastric dilatation, which is a common occurrence and not infrequently fatal. Treatment was with suction via a nasogastric tube. Antibiotics were liberally given in the postoperative period. The urine output was maintained at 1.5 liters per day at least.

Summary

The primary urologic problem in postpoliomyelitic patients in respirators is urinary tract calculus formation. The problem has two phases: the prevention of calculi by medical means and the treatment of calculi already present by either conservative or surgical means. Major urologic surgery in the renal fossa has been performed seven times in five patients who were in the lateral position and under endotracheal anesthesia. All patients did well during surgery and in the postoperative period. With the proper indications, and with the urologist working in close cooperation with the anesthesiologists and pulmonary specialists, postpoliomyelitic patients in respirators can undergo major urologic surgery successfully.

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POPULATION SCREENING FOR UTERINE CANCER BY VAGINAL CYTOLOGY

PRELIMINARY SUMMARY OF RESULTS OF FIRST EXAMINATION OF 108,000 WOMEN AND SECOND TESTING OF 33,000 WOMEN

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• *The method of exfoliative cytology introduced by Papanicolaou and Traut was applied to material obtained by vaginal aspiration from 108,000 women in Shelby County (including Memphis), Tennessee, for the purpose of detecting various types and stages of carcinoma. The preparations for this large-scale screening program necessarily included an extensive educational campaign and required the cooperation of many organizations. Results were reported to the physician who obtained the smears; he in turn informed the woman tested. A woman whose smears showed suspicious cells was advised to have this examination repeated and to have tissue studies in addition. Of the 108,000 women, 33,000 were examined a second time and more than 8,000 a third time.*

The program so far has resulted in the finding of 393 intraepithelial carcinomas, of which 353 had not been suspected, and 373 invasive uterine cancers, of which 112 had not been suspected. The program is also expected to yield new data on etiological factors and on the relation of preinvasive to intraepithelial lesions.

Recent reports indicate that certain factors such as inflammation, endocrine disorders, and pregnancy appear to influence the frequency of uterine cancer, particularly cervical cancer.[1] However, until there is available more specific knowledge concerning the cause or causes of uterine cancer that can be applied as a means for prevention, the direction of efforts toward the early detection, diagnosis, and treatment of this disease while it is still in localized or incipient stages appears to offer the greatest hope for reducing mortality. It is well known that such cancers, when detected in early or localized stages, can be cured. Some cancers, particularly those on or near the surface of the body, are readily detected because of their mass. Others in their early development grow deep to outer cell layers and do not reveal their presence by their mass or by surface change. The latter can be recognized grossly only when they reach the stage where there are apparent surface changes or when symptoms develop. It is well known that this is especially true of cancer of the cervix uteri and that, in its early stages, cancer of this organ is not usually evidenced by gross surface change or clinical symptoms. Prior to the development of techniques of exfoliative cytology, biopsies revealed these early lesions only incidentally or occasionally when gross findings or symptoms were present that led to a suspicion of cancer.

From the University of Tennessee and the National Cancer Institute.

The method of exfoliative cytology introduced by Papanicolaou and Traut[2] in 1943 offered a simple means of finding cellular evidence of cancer in the genital tract. The use of this technique also sharpened the focus on the lesion known as intraepithelial (in

situ) carcinoma of the cervix by detecting this condition in many women who had no signs or symtoms of disease. This brought further attention to the possibility of finding localized disease when it was not recognizable by other procedures. The usefulness of exfoliative cytology as an aid in the diagnosis of cancer of the uterus, bronchus, and stomach has been well attested. It is clear that this method is especially adaptable for examination of the female genital tract because of the simplicity of taking specimens and the ease of follow-up study by biopsy.

It appeared to us that exfoliative cytology might be put to greater use than simply as a diagnostic aid for women with symptoms. Earlier studies of screening by this method of smaller groups of apparently unselected women have had both favorable and unfavorable results.[3] It was our belief that, if this method were applied effectively to a large, unselected group of women, it would be possible to detect cancer at the curable phase and also to learn much about the relationship of so-called intraepithelial carcinoma to cancer. If this method could be used to find preclinical, localized cancer in large groups of apparently well women, the technique could be applied as a screening procedure; the majority of women in such a population could thus be assured that there was no evidence of uterine cancer, while the small group that should be further evaluated by another smear examination and by tissue study for the purpose of definitive diagnosis could be determined. It was essential, as in any test for cancer, that the method should not miss many women with cancer. If many women were incorrectly told that they showed no evidence of cancer, the false reports and false security resulting could bring this approach into disrepute. It was not considered essential, however, for the results of such a screening procedure to be positive only when cancer is present, for women whose smears are found to be suspicious by cytological tests can be studied adequately by cervical biopsy, endocervical curettage, cold knife conization, or diagnostic endometrial curettage as indicated. The group of false-positive results, however, should be kept reasonably small.

Method of Study

With the above facts in mind, we set out to determine how the methods of exfoliative cytology could be applied to the women of Memphis and Shelby County. We had two objectives: to determine the feasibility of using exfoliative cytology as a method for the early detection of cancer and intraepithelial carcinoma and to study the natural history of cancer of the cervix. At the beginning of this study, there were 165,000 women over 20 years of age in this area. It is estimated that this number is now closer to 200,000. We proposed to examine as many of these women as possible by a single vaginal examination and to reexamine them at least three times at intervals of at least a year. In all women whose smears showed suspicious cells, tissue studies were advised as a yardstick to measure the efficiency of the cytological method and as a basis for definitive pathological diagnosis.

The project is a joint effort of the University of Tennessee and the National Cancer Institute. As the first step, the approval and cooperation of the Memphis and Shelby County Medical Society and the participation of the Memphis and Shelby County Health Department were obtained. The local units of the American Cancer Society have also been sponsors. The cooperation of these agencies and especially the increasingly enthusiastic participation of physicians of this area have been essential in carrying out the study.

The cytological laboratory was organized to process and prepare reports on approximately 1,000 to 1,800 smears per week, as described previously by Dunn and Sprunt.[4] Vaginal aspiration was chosen as the method of obtaining the smear rather than one of the cervical procedures because of the accessibility and ease of obtaining specimens, simplicity of this technique, and its applicability to mass screening. The use of scraper, aspirator, swab, or sponge for the purpose of removing cell specimens from the cervix would require insertion of a speculum. The arguments in favor of the latter approach were that this would also require and permit visualization of the cervix by the physician and that a smear made from the cervix would make a greater number of cells available for examination. It has been previously emphasized by Cuyler[5] that examination of cervical specimens has yielded a higher degree of accuracy and that vaginal pool specimens alone could fail to contain cells from a significant number of both invasive and intraepithelial carcinomas. On the other hand, Graham[6] and others have reported excellent results with use of this latter method in hospital and clinic practice.

A significant argument for the obtaining of smears by vaginal aspiration was that no instrumentation would be necessary. This in itself would, we believe, attract a larger number of women, and an essential aim of this screening program was to reach the largest number of women possible. Furthermore, the finding of a sufficient number of physicians to make the examinations in a mass survey such as this would be a prodigious problem, and use of the vaginal specimen makes it possible for trained technicians to obtain the smear in the clinics established for this purpose. Thus, as a procedure for mass screening, the examination of smears obtained by vaginal aspiration was the method of choice, and it has been used in this study. Our experience to the time of writing, reviewed in this report, confirms the advantages of this choice.

One of the major tasks in initiating this project was to inform the women of Memphis of the opportunity afforded by this program and of the significance of the cytological examination of the vaginal smear. An essential phase of this program was to stimulate essentially well women to consider the prevention of clinical uterine cancer as a personal problem. The publicity consisted of an educational campaign designed to explain the value of this examination in the detection of unsuspected early uterine cancer in the presymptomatic stage in order to prevent the development of incurable cancer. Dissemination of information concerning this cancer survey project has been continuously aided by the excellent cooperation of local newspapers and radio and television stations. An ex-

tensive program of talks, including discussions concerning uterine cancer, cytological examination, and the objectives of this program, was arranged for women's church organizations, parent-teacher groups, and women's clubs and in industries and at business sites where temporary clinics were to be set up. The plans for all public relations were considered and approved by a committee appointed by the Memphis and Shelby County Medical Society. As a result of this close liaison with the county medical society, there has been excellent cooperation by the physicians of this area.

As previously described,[4] smears have been obtained both from women visiting physicians of this area and from those attending the clinics established for this purpose. At present, approximately 50% of the smears are received from the more than 300 participating Memphis and Shelby County physicians, while 50% are sent in by the special clinics set up in hospitals, health centers, 31 city and county school clinics, and 60 industrial or business sites. The clinics in schools and business centers are temporary clinics that are opened annually wherever there are 50 or more women. Such clinics are set up for from a few hours to three days, depending on the number of women.

The results of the examination are reported to the physician who obtained the smears, who in turn informs the woman tested. Reports are under no circumstances made directly to the women. When testing is done in the special temporary clinics in schools or industrial sites, each woman examined is requested to indicate her personal physician, to whom the report is to be forwarded. If findings indicate the need for follow-up studies, women unable to assume costs are referred to the special gynecologic clinic at a Memphis hospital that is maintained by the staff of the division of obstetrics and gynecology of the University of Tennessee for this purpose.

Classification of Smears.—In our laboratory, smears are classified as follows: type 1, normal; type 2, abnormal cells present, possibly suspicious; type 3, abnormal cells present, moderately suspicious; type 3a, cells possibly indicative of intraepithelial carcinoma; type 3b, cells indicative of intraepithelial carcinoma; type 3c, very abnormal cells, possibly indicative of invasive cancer; types 4 and 5, cells indicative of cancer. Specific diagnoses are not given to the physician. Instead, four types of reports are made: 1. Satisfactory: the physician is advised that this report means the patient can be told that no evidence of cancer was found but she is to be advised to return in a year. 2. Unsatisfactory: this report means the smear was not adequate for diagnosis. 3. Advised further study: this report indicates that the smear by our classification was a type 2; that is, a few suspicious cells were seen and cervical smear studies are requested. 4. Biopsy recommended: this report means that the smear was classed as type 3, 4, or 5 and that a tissue study is needed for definitive diagnosis.

It is important to emphasize the fact that, to increase the accuracy of this screening technique, all women who had smears classified as type 2 were requested to have further cytological studies. Approximately 3% of the women examined had smears classified as type 2; hence in one sense the vaginal smear is being used to indicate the need not only for tissue study by biopsy but for further cytological study.

Reference to the above method of reporting emphasizes again the philosophy that the cytological method has its greatest value and is being used in this project as a screen for the detection of all suspicious cases that deserve further study and not just as a diagnostic procedure. While it is apparent that the majority of symptomatic invasive uterine cancers will be diagnosed by conventional methods, a significant number of unsuspected invasive cancers are detected by cytology. But it is in the group of preinvasive cervical lesions (epithelial dysplasia, atypical metaplasia of the cervix and endocervix, and especially intraepithelial carcinoma) and asymptomatic invasive cancer that the cytological method is most productive of unsuspected cases that either are cancer or bear watching. This is the reason for our plan to request supplementary cytological examination of vaginal and cervical smears in all women with type 2 smears and to advise tissue study in all those with type 3 to type 5 smears. It is also apparent, however, that it is in women with this borderline group of smears, especially, that the cytological method is not sufficiently specific to diagnose cancer definitively. We believe that tissue study is essential for definitive diagnosis.

Results in 108,000 Women Examined Once

Up to the time of writing, more than 108,000 women have been examined once, 33,000 of these same women a second time, and over 8,000 at least three times. Previous reports have summarized the progress of this study after examination of 20,000, 60,000, and 80,000 women.[5] This report is concerned with the results in the first 108,136 women tested once and the first 32,728 who returned for a second examination.

The study reported here was completed in the three and one-half years ending December, 1955. The testing of half of the female population of this metropolitan area in this period tells the story of response obtained and answers the important question of how many women can be reached. It should be emphasized that this preliminary report includes data concerning specimens sent to the project laboratory from private physicians as well as from the special clinics of this area; thus, approximately 13% of the women examined were not residents of Shelby County, the designated test area. Further analysis with reference to residence, race, age, and source of specimens is now being carried out.

In 983 of each thousand women examined on first screening, no evidence of cancer or significant abnormality was found in the screening cytological study, while 17 of each thousand were advised to have further study by biopsy. (An additional 163 women were asked to return for repeat smear examinations because of unsatisfactory smears or minimal cytological change [type 2 smears]. Approximately 50% of the 163 did not return.) In table 1 it is seen that approximately 13 (77%) of the 17 women in each thousand for whom biopsies were requested did return. Of these 13

women, 8.6 were found to have some pathological change: 7.3 had intraepithelial carcinoma or cancer, and the remaining 1.3 showed a marked degree of atypical change that was considered to be a borderline lesion or possible intraepithelial carcinoma.

TABLE 1.—*Pathological Findings in 1,453 of 1,842 Women for Whom Biopsies Were Recommended as a Result of Examination of Vaginal Smears of 108,136 Women*

	No.		% of 108,000 Women
Invasive uterine cancer	373		0.34
Cancer of cervix		331	0.31
Cancer of corpus		42	0.04
Other genital cancers	20		0.02
Intraepithelial carcinoma of cervix	393		0.36
Total cancer and intraepithelial carcinoma	786		0.73
Atypical metaplasia	141		0.13
Findings normal	479		0.44
Total	1,406*		1.30

*Biopsies were inadequate in 47 women.

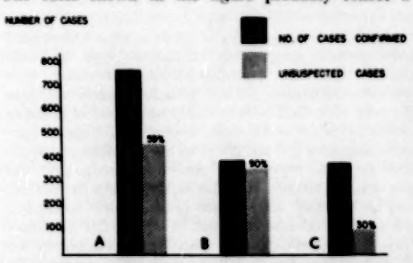
The very atypical epithelial metaplasia (which might show possible intraepithelial carcinoma) referred to in table 1, is important and significant; women with this type of lesion deserve careful follow-up study. If, as we believe, intraepithelial carcinoma is merely a stage in the sequentially developing process that, at least frequently and possibly always if left alone, leads to cancer, then its precursor, atypical epithelial metaplasia, is just as important to label, both for the prevention of uterine cancer and for study in furthering knowledge of the life history of this process. Obviously, too, because the pathological limits of intraepithelial cancer are arbitrary and cannot always be sharply defined and because interpretation is sometimes dependent on incomplete tissue samples, many of this group can be considered as merging with those lesions interpreted as intraepithelial carcinoma.

While the finding of four cases of intraepithelial cervical carcinoma per thousand women (0.36%) is believed to be an index of frequency of this lesion in the group that was screened, the rate of occurrence of invasive carcinoma as found in this survey probably does not represent an accurate index for this area. The latter data must be corrected by a morbidity survey that will be done to determine the number of women with clinically recognized cancer who did not have smears examined and thus are not included.*

Distribution According to Residence and Race.—The data concerning these 108,000 women are subject to review in a number of ways and, as previously indicated, will be analyzed and adjusted for age, race, and resident status and reported in detail at a later date. However, it is possible to discuss some of these factors at this time. While this survey is aimed primarily at residents of Shelby County, it would have been difficult to exclude persons not living in Memphis who come to Memphis physicians for their medical care. It is of interest to note that 134 (36%) of the 373 women with invasive uterine cancer were nonresidents, although nonresidents constituted only 13% of the women who were examined. While the figure of 239 cases of invasive cancer in residents is low and will be corrected by determining the number of additional cases of invasive cancer not seen in this study by a supplementary morbidity survey, these data give a crude rate of invasive cancer for the women of Memphis and Shelby County of 2.5 per thousand compared to 9.6 for the nonresidents. It is obvious that a significant number of the women coming to Memphis for examination had symptoms and may be said to have had their cancer diagnosed by conventional methods. This emphasizes the fact that the nonresidents were a selected group such as will be found in any hospital sampling. On the other hand, the rate of occurrence of intraepithelial carcinoma was similar for the two groups, as would be expected for this predominantly asymptomatic and unsuspected lesion.

Another important factor for analysis is the race incidence. Half of the cancers that were found were in Negroes, who constituted one-third of the surveyed population. This ratio was expected as shown by a morbidity survey for uterine cancer for this area for 1950 and 1951,* in which an incidence rate of 80 to 52 cases and a prevalence rate of 120 to 82 per 100,000 of Negro to white was found. Of interest is the fact that two-fifths of the intraepithelial carcinomas were found in the Negro women representing approximately one-third of those seen. These data are now being analyzed further with respect to source of specimen, i.e., whether it is from a private physician, health clinic, medical institution, industrial clinic, or city hospital clinic, to determine the comparative prevalence, especially of intraepithelial carcinoma, in these different groups.

Number of Unsuspected Cases Found.—Of particular interest in evaluation of the use of cytological screening for prevention of clinical cancer has been the question directed to the physician in each case, "Would a biopsy have been performed at this time if the smear had not been done?" It will be apparent that the number of unsuspected cases diagnosed is the most significant single criterion now available to us in assessing the value of this method in mass screening. The rates shown in the figure probably reflect a



Comparison of number of unsuspected cases of intraepithelial carcinoma of the cervix and cancer and the total number of confirmed cases. *A*, total invasive cancer and intraepithelial carcinoma; *B*, intraepithelial carcinoma of the cervix; *C*, invasive cancer.

minimal figure, for it is likely that the publicity and educational program that were part of this project brought some of the patients with symptomatic cancer to their physicians at an earlier date than otherwise.

In the figure it is seen that 463 (59%) of the 786 cases of invasive cancer and intraepithelial carcinoma were unsuspected. We believe this to be a most sig-

nificant and encouraging fact relating to the value of this program. Diagnosis in these women is directly attributable to detection by smear. This represents an unsuspected-case-finding rate of practically five women in a thousand. That the majority of the intraepithelial carcinomas would not otherwise have been discovered (353 of the 393 were unsuspected) was expected. It is interesting to note that the finding of unsuspected cases is not limited to this group of intraepithelial carcinomas, which are predominantly asymptomatic and not recognizable grossly. One hundred twelve (30%) of 373 cases of invasive neoplasia were labeled by the participating physicians as unsuspected (see figure).

Age Distribution.—The age distribution of women with uterine neoplasms is of special significance in indicating both the age groups that should be surveyed and how frequently testing should be done. Analysis to date indicates that the peak incidence of intraepithelial carcinoma is in women of from 30 to 34 years of age. This finding confirms the view that women 20 years of age and over should be included in any survey the purpose of which is to find this disease in its early stages. The apparent spread between the peak incidence of intraepithelial carcinoma in women from 30 to 34 years of age and that of invasive cancer in women from 50 to 54 years of age again supplements the previous evidence to the effect that, if, as is now generally accepted, intraepithelial carcinoma represents a stage in cervical carcinogenesis, it may take years to develop. It should be added that the data concerning age distribution are being analyzed with respect to the influence of the number of women in each age group as well as their race and place of residence.

Results of Reexamination of Thirty-Three Thousand Women

The second part of our plan provided for the reexamination at approximately yearly intervals for at least three years of as many as possible of those women examined once who were found to have no evidence of intraepithelial carcinoma or cancer in the first screening survey. It was our belief that this second phase of the study could contribute significant facts about the natural history of uterine cancer, with special reference to the more common squamous cell carcinoma of the cervix. When the incidence of new cases in an already screened population is known, the quantitative relation of intraepithelial carcinoma to cancer should be evident. Finally, such data concerning rescreening and a subsequent morbidity survey should indicate, by the number of preinvasive lesions and clinical cancers found as compared to the number found in the first survey, the effectiveness of this approach to control of uterine cancer in shifting the predominance from clinical to asymptomatic cancer. A brief summary of the methods, problems, and results of our efforts in the recall of the women for reexamination has been reported elsewhere.[7]

Table 2 shows the results of this second screening of 32,728 women. It is seen that, at the time of writing, only 244 (69%) of the 353 biopsies recommended had been performed. It is expected that in a few more months this percentage will have increased to at least the 79% of the first screening. In this table it is also shown that 83 intraepithelial carcinomas or cancers were found; 72 of them were intraepithelial carcinomas, 9 were invasive cancers of the cervix, and 2 were cancers of the uterine body.

It is of interest to compare the case-finding rates for the second screening with those for the first. Of each 1,000 women examined in the first screening, 3.6 were found to have intraepithelial carcinoma and 3.1 invasive cancer of the cervix. In the second screening, of each 1,000 women, 2.2 had intraepithelial carcinoma and 0.3 had invasive cancer of the cervix. It is believed that, when adjustment is made for differences with respect to race and age distribution between the women in the first and second screenings, the reduction in case-finding rates will be increased.

TABLE 2.—*Pathological Findings in 244 of 353 Women for Whom Biopsies Were Recommended as a Result of Second Annual Examination of Vaginal Smears of 32,728 Women*

	No.		% of 33,000 Women
Invasive uterine cancer	11		0.032
Cancer of cervix		9	0.030
Cancer of corpus		2	0.002
Intraepithelial carcinoma of cervix	72		0.218
Total cancer and intraepithelial carcinoma	83		0.254
Atypical metaplasia	45		0.136
Findings normal	109		0.330
Total	237*		0.700

*Biopsies were inadequate in 7 women.

Reliability of Vaginal Smear as Screening Procedure

One of the more important problems in this study is how many cancers are missed by this screening procedure. A precise figure cannot be given until a sizable group of women has been examined three times. Our first precaution against error is through close contact with the physicians and hospitals. All cases of cancer of the reproductive tract are called to our attention. Since the onset of this survey there have been, among the women whose smears were classed as type 1, 13 intraepithelial carcinomas of the cervix, 11 squamous-cell carcinomas of the cervix (invasive), 6 adenocarcinomas of the uterus (corpus), and 8 cancers of other parts of the reproductive system. When the smears from these 38 women were reexamined, 19 were again classed as normal. The reason for this is not clear, but we consider it a sampling error; that is, there were too few suspicious cells in the vaginal pool for one to show up in the sample placed on the slide. Of the remaining 19 smears, 4 should have been classed as unsatisfactory; 6 were definitely errors, as suspicious cells were seen when these slides were reexamined, and biopsies should have been requested; and the remaining 9 in retrospect were classified as type 2—in other words, a few abnormal cells were seen.

Our second approach to the problem of error is through the reexamination of the smear made at the first screening of all those who had cancer or intraepithelial carcinoma at the time of the second examination. In table 2 it is seen that there were 72 women

with intraepithelial carcinoma of the cervix. Of these 72 women, 28 had smears that had been read as normal on the first survey and were normal when reexamined. Twenty-one of these had an intraepithelial lesion and five had cancer. Thus, this group would appear to include the patients who had developed cancer since the first smear was taken. However, the possibility exists that the lesion was present and the vaginal sample failed to include cells representative of a lesion. Of the remaining 46 smears, 6 that were originally called normal should have been classified as suspicious (type 3 or 3a), and a biopsy should have been recommended. In another six women the original smear was type 2, and further cytological study was recommended but not done. Thirteen were called normal by the screening technicians and on review were reclassified as type 2, and these should have been studied further. Fifteen were originally called cytological types 3, 4, or 5, and biopsies were recommended, but seven of these women failed to have biopsies done; of the other eight, six had a tissue diagnosis of atypical metaplasia, in one the biopsy showed no abnormal change, and in the other biopsy was inadequate. Lastly, there were six smears that, it is now thought, should have been called unsatisfactory for adequate evaluation.

Thirdly, and perhaps most important, the *esprit de corps* of all workers in the cytology laboratory is kept high by keeping them informed of all phases of the study, so that they realize the results of a failure to mark a suspicious cell.

Comment

In this report, the term intraepithelial carcinoma has been used as synonymous with "in situ" as used by many. The histological and cytological features of this controversial lesion have been repeatedly discussed by many authors.[9] We agree that the essential features are that it is predominantly a lesion of the squamocolumnar junction or the endocervix and that cytologically it mimics cancer to greater or lesser degree and histologically involves and is limited to the epithelial surface or endocervical glands without invasion of underlying stroma. It is but one segment of the dynamic biological process of cervical carcinogenesis. We believe that its borders cannot always be sharply defined, and it must be recognized that the limits of pathological definition are dependent on personal experience and correlative study.

No attempt will be made to discuss the arguments for or against the current trend to accept this lesion as a preinvasive stage of cervical cancer. Suffice it to say that the experience of any critical observer reveals that this lesion is frequently associated with invasive cervical carcinoma and that the available evidence indicates that intraepithelial carcinoma may often be preinvasive cancer. Thus, intraepithelial carcinoma is now generally accepted as significant in relation to cancer of the cervix whether or not it is a potential or a preinvasive stage of the common squamous cell carcinoma of the cervix. Yet it is equally clear that the exact biological story is not known, and there are still insufficient data to indicate how often this sequential progression takes place or what percentage of cancers develop from reserve cell hyperplasia of endocervical or junctional areas to atypical metaplasia of varying degrees to intraepithelial carcinoma; that is, from surface, preinvasive carcinoma to invasive cancer.[10] The removal of these intraepithelial carcinomas and cervical cancers from a population to be examined annually has provided this investigation with the experimental stage to test the thesis that the lesion known as intraepithelial carcinoma of the cervix is the preinvasive stage of invasive cervical carcinoma.

We believe that further investigation, analysis of the data concerning the rescreening to determine the age-specific incidence of development, and the follow-up of the significant number of patients with what may be cancer in its early stages should contribute evidence to indicate more exactly the relationship of the cervical epithelial changes that lead to invasive cancer and enlighten this hazy but important controversial question. Though the biological story of this relation or its frequency is not yet fully elucidated, the available evidence clearly justifies and dictates judicious application of this knowledge to efforts directed toward prevention of or decreasing the morbidity and mortality of uterine cancer as in this project. Thus we have proceeded with the plan of this project on the thesis that the developmental stages of atypical metaplasia, dysplasia, and intraepithelial carcinoma were significant in relation to uterine cancer.

It is obvious (see figure) that the value of this or similar screening efforts is economically dependent on this relation, for the preponderance of unsuspected cases (77%) are of intraepithelial carcinoma. If intraepithelial carcinoma is not the forerunner of cancer in a significant percentage of cases, the cost would undoubtedly prohibit widespread use of cytological examination of vaginal smears as a screening procedure, for it would not pay the community to find only the smaller number of unsuspected invasive cancers, even though it would be advantageous to the individual involved.

It is of interest to compare the number of intraepithelial carcinomas diagnosed in residents of Shelby County in 1950 and 1951 [4] to the number (465) found in the 108,000 women during the three and a half years of this project. Diagnoses during both periods were made by the same pathologists. More than a fourfold increase resulted from this large-scale application of cytological methods. A similar comparison cannot be made with invasive uterine cancer until another morbidity survey is completed to furnish data concerning cancers detected by means other than cytological screening.

Efforts were directed in our program to guard against false security as well as misunderstanding of the scope of the test. Each woman having the test has received a memorandum including the following statement: "Remember that this test detects cancer in the uterus (womb) only; it is not a test for cancer in other parts of the body. All women over 20 should have this test once a year as a health safeguard, like a chest x-ray. If symptoms should develop before your next test, see your doctor—don't wait." However, this effort in no way decreases the importance of the study of incidence of false-negative tests as a significant factor

in evaluating the reliability of this approach. As previously discussed, supplementary information will be obtained from the repeat annual studies, so that restudy of at least three annual tests will be available for an accurate measure of reliability. Data now available not only indicate that the false-negative error is low for the first examination but suggest that the possible error disappears for all practical purposes if women are examined at yearly intervals.

The great advantage of the plan used in the Memphis project for this community is that, even though this is a mass project, the close doctor-patient relationship has been maintained throughout for follow-up diagnostic studies or treatment as indicated. Every effort has been made to maintain and foster this relationship between the women examined, their doctors, and the pathologists interpreting the cytological tests and tissue studies.

Until further knowledge permits efforts directed at prevention of cancer, this and similar investigations in cancer research are aimed at decreasing the incidence of incurable malignancy and at the prevention of deaths from cancer. Here attention has been directed at prevention of incurable disease by careful cytological examination, early diagnosis while the disease is still in a curable stage, and, thus, early treatment.

This program tests the thesis that, by detection and removal of intraepithelial and incipient cancer of the uterus, the situation can become one where cancers are found predominantly in the preinvasive and preclinical stage rather than in the symptomatic and frankly invasive stage. The trend indicated by the case rate for the 33,000 women (table 2) suggests that this approach to control of uterine cancer can be successful, but final conclusions cannot yet be drawn.

The trend indicated in this preliminary report offers evidence that suggests that this approach can be successful and that the present situation, where most cases are discovered at the symptomatic stage, which is usually too late for successful treatment, can be changed to one where the majority are found at the presymptomatic or localized stage, a stage at which available evidence indicates the cure rate can be very high. The final answer and measure of success of this approach will be determined by continuation of this study to determine changes in morbidity and mortality from this disease in this area.

Summary

A plan was devised for the screening of a whole population for the early detection of cancer of the uterus. Among the 108,000 women examined for the first time there were 393 intraepithelial carcinomas; of these, 353 (90%) had not been suspected. There were also 373 invasive cancers of the uterus, of which 112 (30%) were unsuspected. This shows clearly the value of this procedure as a method for the early detection of cancer. On the second examination of 33,000 women, 2.2 with intraepithelial carcinomas were found per thousand, as compared with 3.6 on the first examination, while the rate for invasive cancer was reduced from 3.4 to 0.3 cases per thousand women. These changes are related to the natural history of cancer.

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Growth Retardation in Renal Disease.—In an effort to determine a common denominator for the growth failure of renal disease, the clinical and laboratory observations on 41 children with chronic renal disorders have been surveyed. Twenty-one of the patients had growth retardation. Of the manifestations investigated, none met the criterion of being universally present in the stunted patients and absent in children growing normally. Failure of renal concentrating ability was present in all children with growth failure, but failure of concentration was also observed in a few children growing normally. On the other hand, chronic acidosis was never observed in children growing normally but was present in only 76% of the retarded children. There was no evidence that mild azotemia, albuminuria, or chronic urinary tract infection significantly affected growth. The advent of chronic acidosis in a patient with renal disease appeared to cause stunting by producing temporary growth arrest. After stature had become subnormal, growth was resumed at a slow rate, although acidosis continued to be present. The role of low caloric intake resulting from anorexia as a cause of growth retardation in renal disease can only be assessed roughly in the present study by the weight-for-height index. According to this assessment only eight of the retarded children fall into the category of hypocaloric dwarfs. Two other children demonstrated a growth spurt after establishment of adequate urinary drainage by surgery, indicating that their dwarfism might also have been a result of low caloric intake. It was found that between the two factors of low caloric intake, as assessed by the above methods, and chronic acidosis, the growth retardation of nearly all the patients in the present series could be accounted for.—C. D. West, M. D. and W. C. Smith, M. D., An Attempt to Elucidate the Cause of Growth Retardation in Renal Disease, *A.M.A. Journal of Diseases of Children*, May, 1956.

CHLORPROMAZINE IN THE TREATMENT OF PORPHYRIA

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• *Chlorpromazine was administered by mouth, generally in doses of 25 mg. three or four times daily, in nine cases of intermittent acute porphyria with pain and other serious symptoms. This dosage sufficed to control the symptoms in most cases, although it did not cure established paralyses. In three of the patients a single dose of 100 mg. of chlorpromazine was followed by complete clinical remission. The first effect was a relief of the nervous symptoms, including the pain; this improvement was not correlated with any significant changes in excretion of porphyrin or porphobilinogen during the period of study. The drug appeared to interrupt a vicious cycle, after which the patient was able to regain a state of remission spontaneously. Chlorpromazine has been the most consistently effective remedy thus far available for the pain and nervous manifestations of porphyria.*

To date, no agent has been found that will correct the metabolic defect of porphyria. Certain ganglioplegics, corticotropin, and hydrocortisone or its analogues have been thought, in some cases, to interfere with the progress of acute attacks of porphyria. However, the response is extremely variable, and, because of the occurrence of spontaneous remissions, conclusions have not been possible. An important factor in the evaluation of any agent in the treatment of porphyria is the possible aggravation of the disease by the chemical. Thus, it is well known that barbiturates and certain other chemicals can precipitate attacks of acute porphyria in individuals with latent disease.[1] This fact indeed has made one especially conservative about a trial of new agents. Our own experience with the use of tranquilizing agents has undoubtedly been retarded because of concern at the outset that we might do more harm than good. However, the great difficulty encountered in treating cases of porphyria induced us to make trials of some of the newer agents. Our actual point of departure was the idea of enhancing the effect of meperidine (Demerol) hydrochloride or of diminishing the required amount.

The purpose of the present report is to describe experience during the past year with the use of chlorpromazine and, to a lesser extent, the Rauwolfia alkaloids in cases of intermittent acute porphyria. Nine cases are included in this report. Six of these were studied at the University of Minnesota and Minneapolis Veterans hospitals. The clinical protocols and results of chlorpromazine therapy in three cases have been made available to us by physicians in other cities.

Report of Cases

Case 1.—A 36-year-old female was admitted to the University of Minnesota Hospitals on Feb. 3, 1956, complaining of severe, crampy abdominal pain. She had been in good health until Jan. 7, 1956, when she had begun to have attacks of vomiting and abdominal pain and passed dark urine. The patient was hospitalized elsewhere and received parenterally given fluids, narcotics, and barbiturates. Because of persistent abdominal pain, an exploratory laparotomy was performed on Jan. 22, 1956, at which time a normal appendix was removed. Her symptoms continued, and on Feb. 4, 1956, the urine was first found to be positive for porphobilinogen. The diagnosis of porphyria was made by Dr. D. S. Morris, Winston-Salem, N. C., who referred the patient to us.

Physical examination revealed abdominal tenderness without rigidity or distention and diminished posture sense of the lower extremities. Four days later the left biceps reflex was absent, and there was transient mild weakness of the left arm. The amounts of urinary porphyrin excreted daily are shown in figure 1. On Feb. 6, 1956, the patient's abdominal pain promptly abated after the intramuscular administration of 50 mg. of chlorpromazine. At the same time she began to eat and said she felt well for the first time since the onset of her illness. Because of recurrence of abdominal pain, chlorpromazine was given orally in gradually decreasing amounts, as noted in figure 1. Therapy was discontinued on Feb. 18, 1956, and the patient was discharged two days later without symptoms.

The patient has remained in good health up to the present time. Recently urinary porphyrin and porphobilinogen excretion studies were made. The porphobilinogen excreted in the urine was 28 units in 24 hours; the coproporphyrin excreted was 370 mcg. in 24 hours; and uroporphyrin excreted was 1,560 mcg. in 24 hours. A comparison of these values with the final daily excretions represented in figure 1 shows little change except that the excretion of coproporphyrin has diminished.

Case 2.—A 69-year-old female who was known to have had hypertension for three years was admitted to the University of Minnesota Hospitals on Sept. 27, 1955. Four weeks prior to admission, she had developed tremor and agitation and had been placed on mephobarbital (Mebaral) therapy. Shortly after this she began to have abdominal pain, nausea, and vomiting episodes and passed port-wine-colored urine, which was found to be positive for porphobilinogen by Dr. H. A. Christianson, Jackson, Minn. Physical examination on admission revealed grade-2 hypertensive retinopathy, cardiac enlargement, and a tender, distended abdomen. The blood pressure was 190/120 mm. Hg. One freshly voided specimen of urine was positive for porphobilinogen, and all subsequent specimens were negative. Data on the urinary porphyrin excreted daily are given in figure 2. Chlorpromazine was administered in amounts of 25 mg. four times daily for four days, during which time the abdominal pain gradually subsided. On the fourth hospital day the patient had one brief recurrence of abdominal pain, which quickly disappeared and did not recur. Chlorpromazine was withdrawn on Oct. 24, 1955, and the patient was discharged asymptomatic on Oct. 28, 1955.

Case 3.—A 66-year-old male was first admitted to the Minneapolis Veterans Hospital in 1951. Intermittently for 11 years he had had abdominal pain and hypertension and passed dark urine and had experienced a change in personality. At that time the diagnosis of intermittent acute porphyria was first established. He had had remissions while on corticotropin therapy on two occasions. In the fall of 1955, he had received prednisone without benefit but had had fleeting relief of abdominal pain on pentolinium therapy. At that time meperidine hydrochloride was withdrawn (the patient was strongly addicted). After a period of delirium, for which he was given large doses of reserpine (1 to 2 mg.), he became more lucid and tractable. Reserpine was withdrawn, and within a short time the patient

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experienced a severe exacerbation of generalized aching and abdominal pain associated with dark urine and anasarca. Pleural effusions were present, the blood pressure was 240/120 mm. Hg, and ileus with abdominal distention was noted. The patient was placed on a combined chlorpromazine (50 mg. four times a day) and reserpine (0.25 mg. four times a day)

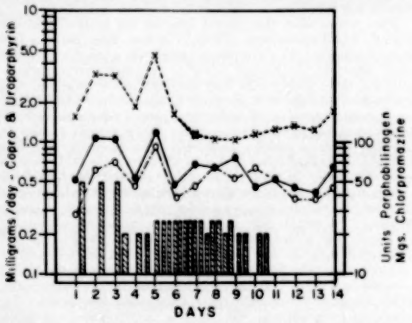

Fig. 1.—Daily excretion of urinary porphyrin and porphobilinogen plotted on a semilogarithmic scale during administration of chlorpromazine. Dosage is shown as divided through 24-hour periods. Levels of uroporphyrin are indicated by X's connected by broken lines; of porphobilinogen by O's connected by long and short lines; of coproporphyrin by black dots connected by unbroken lines.

regimen with apparent marked relief of abdominal symptoms, tremulousness, and agitation. The edema abated. He then had an attack of abdominal pain and generalized aching in December, 1955. Chlorpromazine (50 mg. four times a day) and reserpine (0.25 mg. four times a day) were again given with sustained relief of symptoms. The patient has been relatively asymptomatic without medication up to the present.

This man had been difficult to manage on previous hospitalizations because of his psychotic behavior and extreme agitation during acute episodes of abdominal pain. The tranquilizing effects of chlorpromazine and reserpine were decisive in altering the patient's course and in avoiding the use of narcotics.

Case 4.—A 24-year-old male was admitted to the Minneapolis Veterans Hospital on Aug. 9, 1955, following transfer from another hospital, where he had developed a flaccid quadriparesis. Four months earlier the patient experienced crampy abdominal pain, nausea, vomiting, and constipation, which increased in severity until the onset of quadriparesis. Four years previously he had had an episode of abdominal pain, and his urine had been red intermittently since then. Physical examination on admission revealed flaccid quadriparesis. The excretion of uroporphyrin and coproporphyrin in the urine was markedly increased. The test for urinary porphobilinogen was strongly positive. The paralysis largely abated within a week, with a residual bilateral palsy of the radial nerve. While in the hospital, on Nov. 10, 1955, the patient developed severe abdominal pain, vomiting, and agitation. Corticotropin, prednisone, pentolinium, intravenously given procaine, and tetraethylammonium chloride (Etamon) were all administered individually without benefit. The patient required large doses of meperidine hydrochloride for control of pain. Chlorpromazine in 25-mg. amounts was given intramuscularly at six-to-eight-hour intervals. The meperidine requirement dropped but pain persisted, and on Dec. 8, 1956, the patient was given 100 mg. of chlorpromazine intramuscularly. He became completely asymptomatic within one hour. He was discharged two days later, having required no further medication. He was readmitted on Feb. 9, 1956, with severe abdominal pain and was promptly given 100 mg. of chlorpromazine intramuscularly with immediate and complete subsidence of the attack. At the present time the patient is symptom-free except for the persistence of bilateral wrist drop. In this case, it was evident that the optimal response to chlorpromazine was obtained only after the administration of a large single dose, smaller doses given intermittently being much less effective.

Case 5.—A 23-year-old male admitted in May, 1955, had had crampy abdominal pain, attacks of vomiting, and constipation and had passed dark-red urine for 10 days. He had noted red urine intermittently for one year prior to admission. The blood pressure was 170/110 mm. Hg. The urine was positive for porphobilinogen, and the daily excretion of coproporphyrin and uroporphyrin was markedly elevated. Relief from abdominal symptoms occurred after the administration of pentolinium and corticotropin therapy. Because of severe apprehension and anxiety, he was placed on reserpine therapy (0.25 mg. twice a day) and attained complete relief. On three subsequent occasions the patient stopped taking the medicament, and there was recurrence of extreme nervousness and mild abdominal pain on each occasion. Each time the symptoms abated after the reinstitution of reserpine therapy. On March 19, 1956, he was readmitted to the hospital and given meprobamate (400 mg. three times a day). Within 9 days he experienced moderate abdominal distress and in 18 days developed a full-blown attack of porphyria with severe abdominal pain, vomiting, constipation, and hypertension. Use of meprobamate was discontinued. Chlorpromazine was given (25 mg. three times a day intramuscularly) with moderate relief in two days, and the attack subsided 36 hours after four spaced doses of 100 mg. of chlorpromazine were given intramuscularly.

Daily amounts of urinary porphyrin excreted during therapy with chlorpromazine are shown in figure 3. It is not clear why there should be such an abrupt rise in the excretion of uroporphyrin. A part of this may be artefact on the basis of conversion of porphobilinogen to uroporphyrin after the urine was passed.

The patient's history suggests that use of reserpine may have aborted full-blown porphyric symptoms, in that mild symptoms occurred upon withdrawal of the drug and disappeared on readministration of reserpine. Use of meprobamate did not modify the acute attack, and the drug may even be suspect in its precipitation. Chlorpromazine relieved symptoms when given in relatively large amounts (100 mg.) intramuscularly. The patient is asymptomatic at the present time.

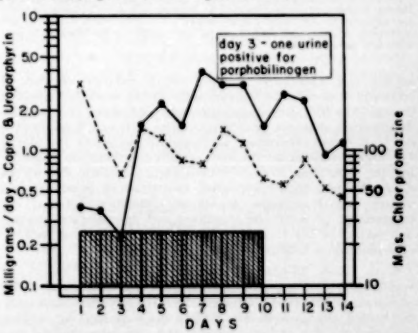

Fig. 2.—Daily excretion of urinary porphyrin plotted on a semilogarithmic scale during administration of chlorpromazine. One freshly voided urine specimen on the third day gave a positive reaction for porphobilinogen. Porphobilinogen was not detectable in the urine after the third day. Dosage is shown as divided through 24-hour periods. Levels of uroporphyrin are indicated by X's connected by broken lines and of coproporphyrin by black dots connected by unbroken lines.

Case 6.—In 1952 a 26-year-old female noted abdominal pain and dark urine. It is of possible interest that the patient had been exposed in her work to the fumes of molten lead for a period of two years before and up to this first outspoken attack of porphyria. An appendectomy was performed in 1952. In June, 1954, the diagnosis of porphyria was established during an episode of abdominal pain, vomiting, and delirium. She was first admitted to Barnes Hospital in St. Louis, on

Nov. 30, 1954, with recurrence of porphyric symptoms, for which she was given small doses of chlorpromazine. A remission occurred. During a second admission on Feb. 23, 1955, a remission was again observed after cortisone therapy. The patient then had severe headaches that disappeared when small doses of chlorpromazine were given. A third admission on Aug. 24, 1955, was occasioned by a recurrence of generalized

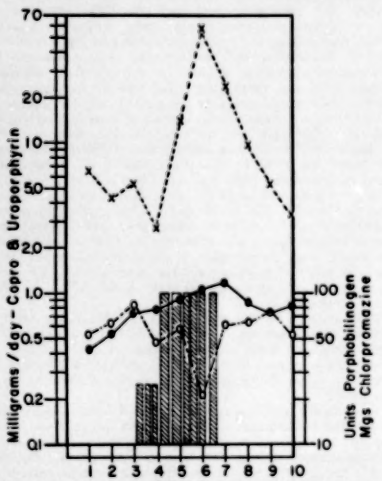

Fig. 3.—Daily excretion of urinary porphyrin and porphobilinogen plotted on a semilogarithmic scale during administration of chlorpromazine. Dosage is shown as divided through 24-hour periods. Levels of uroporphyrin are indicated by X's connected by broken lines; of porphobilinogen by O's connected by long and short lines; of coproporphyrin by black dots connected by unbroken lines.

aching and abdominal cramps, which did not respond to cortisone or prednisone but promptly abated on chlorpromazine therapy. On two subsequent occasions abdominal pain rapidly disappeared after use of chlorpromazine (10 mg. four times a day). A recent recurrence of porphyric symptoms on March 17, 1956, was again treated with chlorpromazine therapy (25 mg. four times a day). Within 24 hours of the increase in dosage she was greatly improved, and within 48 hours she was entirely free from pain. A definite correlation between the exacerbation of porphyric symptoms and psychological stresses was noted. At the present time the patient is feeling well on chlorpromazine therapy (25 mg. four times a day).

CASE 7.—A 35-year-old female had nausea, attacks of vomiting, and crampy abdominal pain in November, 1955. She was hospitalized elsewhere for a short time and was discharged unimproved. The patient was examined by another physician the day of her discharge and was rehospitalized one week, after which she developed a flaccid quadriparesis that was diagnosed as conversion hysteria. She was sent to a state psychiatric institution, where she was said to have diabetes and a gastric ulcer. The patient received isophane (NPH) insulin, 40 units every day, and propantheline (Pro-Banthine) bromide and was on a full ulcer regimen. Her abdominal symptoms improved, and the quadriparesis abated. A few days after her discharge from the state hospital, she came under the care of her present physician and complained of epigastric distress and weakness of the wrists and feet. Physical examination revealed abdominal tenderness and hypertension. The blood pressure was 160/110 mm. Hg. She was given phenobarbital (30 mg. four times daily) and continued on insulin therapy. In one week she returned to her physician complaining of nausea, vomiting, and severe, diffuse, crampy abdominal pain. On physical examination there was abdominal tenderness and bilateral wrist and foot drop. The urine was noted to be port-wine in color. A 24-hour urine specimen was sent to our laboratory. Porphobilinogen was present (54 units). Levels of porphyrins were markedly elevated, with a uroporphyrin concentration of 3,281 mcg. and a coproporphyrin concentration of 306 mcg.

Two weeks after the patient entered the hospital she was placed on chlorpromazine therapy (25 mg. three times a day intramuscularly). Her symptoms completely abated within five days. She was discharged while on chlorpromazine therapy (25 mg. twice daily). She had intermittent leg pain and was referred to us by Dr. R. L. Coultrip, Cooperstown, N. D., and she was admitted on May 29, 1956. The patient continued to have intermittent leg pain, which appears to be related mainly to passive or active exercise associated with physiotherapy. She had had no further abdominal pain while receiving chlorpromazine. In order to determine more exactly the effect of chlorpromazine, it was withdrawn temporarily. Two days later she had severe abdominal pain for the first time in months. It should be noted that she had been receiving ethinamate (Valmid) for a number of days to induce sleep. She had abdominal pain on two successive days relieved temporarily by meperidine. On the third day, because of severe abdominal pain she was given 100 mg. of chlorpromazine intramuscularly, with prompt and complete relief that lasted four hours. The pain then recurred, and 100 mg. of chlorpromazine was again given, with complete relief for six hours. This pattern has been observed on a number of occasions subsequently up to the present writing, and the patient is still under observation. It is at least evident that the relief of pain following chlorpromazine in this case, although prompt and complete, was not as enduring as in the other cases of the series. At present the possibility that other chemicals such as ethinamate may have tended to aggravate the porphyria is being investigated.

CASE 8.—A 35-year-old female had had symptoms of insomnia, irritability, headaches, and severe leg pains since December, 1955. Two first cousins were known to have porphyria (confirmed in this laboratory). The patient's symptoms are greatly increased at the time of her menstrual period, and the urine usually becomes quite dark during menses. At one time the patient was placed on ethchlorvynol (Placidyl) therapy, after which dark urine and porphyric symptoms appeared. She required meperidine hydrochloride and alkaloids of opium (Pantopon) for relief of pain much of the time. Recently the patient was given chlorpromazine, 20 mg. every six hours, and has shown marked improvement, which has been sustained. She no longer requires narcotics or sedatives. A 24-hour urine specimen was collected on May 19, 1956, shortly after the commencement of chlorpromazine therapy. Urinary porphobilinogen and porphyrins were measured in our laboratory. The value for porphobilinogen was 79 units, for coproporphyrin 1,454 mcg., and for uroporphyrin 11,095 mcg. per day. After an interim without further symptoms, an additional 24-hour sample, collected from May 31 to June 1, 1956, contained 1,180 mcg. of coproporphyrin, 8,700 mcg. of uroporphyrin, and 56 units of porphobilinogen.

CASE 9.—A 28-year-old male had what was thought to be a "nervous breakdown" with severe generalized and abdominal pain and intermittent episodes of abdominal pain three years prior to hospitalization on Aug. 20, 1955. Six months prior to this, the patient had had severe constipation that required administration of large amounts of laxative. Physical examination on admission was negative except for the presence of diffuse abdominal tenderness. The urine was noted to be dark red. Because of concomitant pyuria, the patient was thought to have a severe urinary tract infection, and he was then treated with sulfisoxazole (Gantrisin), meperidine, and phenobarbital until Aug. 24, 1955. The first urine sample examined for porphobilinogen was negative, but later specimens were positive. An aliquot of a 24-hour urine specimen was studied in our laboratory. The specimen was collected on Aug. 27, 1955. The porphobilinogen concentration was 24 units, that of coproporphyrin 338 mcg., and that of uroporphyrin 88 mcg. per 24 hours. All these values are only moderately elevated and would accord well with the diagnosis of intermittent

acute porphyria in remission. Chlorpromazine (50-75 mg.) was given on Aug. 24, 1955, and at irregular intervals until Aug. 27, 1955, when it was given orally (50 mg. four times a day). By Aug. 27, 1955, the abdominal pain, constipation, and nervousness had largely abated. The symptoms were controlled while on chlorpromazine therapy, and remission was obtained. In the past nine months the patient has had three attacks of abdominal pain, which have not been treated with chlorpromazine.

Comment

The precise action of chlorpromazine in diminishing or abolishing the clinical manifestations of acute porphyria is unknown. It has been asserted repeatedly that chlorpromazine inhibits the sympathetic diencephalic centers and has certain direct adrenolytic actions.[2] Control of anxiety, hyperkinesis, and reversal of the action of certain psychotomimetic drugs (mescaline and lysergic acid diethylamide) are established effects.[2a] The use of chlorpromazine in intractable pain of malignancy,[3] chronic pancreatitis, causalgia,[4] and many types of pain of visceral origin is accompanied by diminished requirement of narcotics, which Rome believes is not unlike the response to prefrontal lobotomy,[3] in which apparently pain is not abolished, but the patient becomes much less aware of its presence. This does not appear to be the case in those patients with intermittent acute porphyria who have responded favorably to chlorpromazine, as they disclaim any perception of abdominal pain. The striking abolition of the apprehension and agitation of the porphyric state, which often results, is apparently independent of the slow recovery from the disorder of the nervous system that results in paralysis.

There are a few references in the literature to the use of chlorpromazine and the Rauwolfia alkaloids in porphyria. Coulonjou, Pouderoux, and Derouet[6] describe one patient with intermittent acute porphyria with severe abdominal pain, vomiting, and neurological deficit who responded within a few hours, with subsidence of the abdominal manifestations after one dose of chlorpromazine given parenterally. Weakness of muscles also improved. A subsequent attack of abdominal pain, vomiting, and apprehension terminated one-half hour after the administration of chlorpromazine. They concluded that chlorpromazine reduced the duration of attack. Durst and Krembs[7] mention the case of a gravid female who experienced severe hyperemesis and abdominal distress after attempting abortion with intravaginal use of potassium permanganate and whose urine was positive for porphobilinogen. This patient obtained relief following parenteral use of chlorpromazine. Martin and Heck[8] in their review of the cases of porphyria seen at the Mayo Clinic state simply that chlorpromazine had been used with "good results" in some patients with abdominal pain. Muller[9] reported a case of intermittent acute porphyria in a young woman in whom intense abdominal pain, unceasing vomiting, high fever, and severe prostration rapidly resulted in a moribund state. The so-called lytic cocktail, consisting of intravenously given chlorpromazine, meperidine (Pethidine) hydrochloride, and promethazine hydrochloride, was administered for six days, with refrigeration of the patient for the first 36 hours. A complete remission was obtained, and the patient remained well during a three-month follow-up period. Although chlorpromazine was not used as the sole therapeutic agent in this case, our own experience would suggest that artificial hibernation with the production of hypothermia was an unnecessary adjunct. Kark[10] used Rauwolfia serpentina in two cases of intermittent acute porphyria and observed beneficial tranquilizing effects in both instances.

No data have been given as to the alterations in excretion of porphyrin or porphyrin precursor in the urine of any of the patients described in the literature who have been treated with chlorpromazine or the Rauwolfia alkaloids. Our own results bearing on this point are inconclusive. In general, it appears that the beneficial effects of chlorpromazine that we have noted are not correlated with changes in excretion of urinary porphyrin or porphobilinogen. Thus, in case 1, despite subsidence of symptoms shortly after the first dose of chlorpromazine, there was actually a considerable increase in excretion of porphyrin and porphobilinogen, which lasted through the fifth day, and at no time did this excretion fall below the initial level. In case 2 it was of interest that the uroporphyrin-coproporphyrin ratio became sharply reversed soon after chlorpromazine therapy was begun. This reversal has often been noted in the past in remissions of acute porphyria. In case 5 (fig. 3) there was a transitory sharp increase of excretion of uroporphyrin. But, as already noted, this may be due in part, at least, to conversion of porphobilinogen to uroporphyrin after the urine was passed. It is evident that there was no change in the excretion of porphyrin or of porphobilinogen that could be correlated with the patient's improved status. Since it is quite clear from previous studies that in well-established remissions the amounts of porphyrin and porphobilinogen excreted are on the average much less than those during the acute relapse,[1] one must consider that the effect of chlorpromazine therapy is indirect in abolishing the pain and nervousness. It may be that the effect is akin to interrupting a vicious cycle. Once it is interrupted, the patient can regain a state of remission spontaneously. Such a theory would necessarily assume that nervous factors in themselves are significant in precipitating relapse. General experience dating from the early work of Günther[11] tends to support such a concept. Günther emphasized the nervous background of the person with acute porphyria and gave it the name "phorphyrismus," by which he meant a peculiar constitutional instability of the nervous system.

Meprobamate is thought to produce selective blocking of transmission of impulses to interneuronal neurons, muscle relaxation, and mild central depression.[12] Although our experience is too limited to make any definite conclusions, the one patient given the drug because of apprehension experienced increased nervousness and anxiety and developed severe abdominal pain, vomiting, and a striking rise in excretion of porphyrin and porphyrin precursor in the urine while on therapy with the drug.

Summary and Conclusions

In nine cases of intermittent acute porphyria, administration of chlorpromazine has been followed promptly by disappearance of pain and nervous symp-

toms. Established paralyses have been unaffected. In the majority of patients, 25 mg. given three or four times daily appeared to be sufficient to control symptoms, but in three patients a single 100-mg. dose was first followed by complete clinical remission. In one of the three, the effect of chlorpromazine during a subsequent mild relapse of pain was of relatively short duration. No definite evidence has been obtained that a reduced excretion of porphyrins or porphobilinogen is an early effect of chlorpromazine therapy. It is possible that the drug interrupts a vicious cycle, permitting a spontaneous remission to occur.

In two cases Rauwolfia alkaloid has been of value in maintenance therapy. In both instances there was absence of nervous symptoms when the patients were receiving the drug, and there was recurrence when the drug was withdrawn. The present experience indicates that chlorpromazine, in relation to other chemicals, is at least reasonably safe in cases of acute porphyria. There has been no suggestion that its use precipitates a relapse of the disease. It is the most consistently effective remedy thus far available for the pain and nervous manifestations.

Drs. Edward H. Reinhard and Samuel Goldfein, Washington University School of Medicine, St. Louis; Dr. Estle P. Muncy, Jefferson City, Tenn.; and Dr. Thomas D. Johnson, Albany, Ga., gave permission to report cases 6, 8, and 9 respectively.

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CHLORAMBUCIL IN TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA AND CERTAIN LYMPHOMAS

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• *Chlorambucil was administered by mouth in doses ranging from 5 to 30 mg. daily for five to seven weeks, so than an average course amounted to 350 mg. Thirty patients were thus treated for lymphocytic leukemias and various lymphomas. In the largest group, namely, 18 patients with chronic lymphocytic leukemia, 3 patients obtained excellent results, in that the hemoglobin level and white blood cell count returned to normal, the differential count was significantly improved, and hepatosplenomegaly and lymph node enlargement disappeared. Eight other patients of this group obtained good results in that the white blood cell count fell, the hemoglobin level rose, the differential count improved, and the liver, spleen, and lymph nodes decreased in size. Results in cases of lymphocytic lymphosarcoma and Hodgkin's disease were less encouraging. In the dosages used, chlorambucil was practically without side-effects.*

In their systematic investigation of the carcinogenic and chemotherapeutic properties of the alkylating agents, Haddow and his associates of the Chester Beatty Research Institute in England [1] examined a variety of aliphatic and aromatic nitrogen mustards. In the course of their study, they found that certain aliphatic alkylating agents particularly depressed myelopoiesis. This lead to the development of busulfan (Myleran), which has been discussed extensively in recent articles.[2] Administration of certain aromatic alkylating agents, on the other hand, led to a specific decrease in circulating lymphocytes. One of these aromatic nitrogen mustards is chlorambucil [*p*-(di-2-chloroethyl) aminophenylbutyric acid], also called CB 1348. The relationship of chlorambucil to other alkylating agents is shown in the figure. The physical and chemical properties of this agent have been described.[3] Haddow found that in rats chlorambucil inhibited Walker carcinoma 256 in doses that had only slight effect on the white blood cell count of normal rats.[4] Elson [1a] as well as Bollag [5] demonstrated that large doses had a profound effect on the lymphocytes of the rat, causing a rapid fall without substantial influence on the granulocytes. This apparent "specificity" prompted investigation of the use of this drug in those conditions in man in which an abnormal proliferation of lymphocytes is found.

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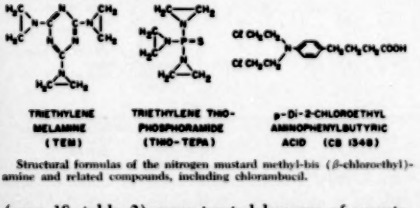
Material and Results

Thirty patients have been treated with chlorambucil at the Francis Delafield Hospital and Presbyterian Hospital since August, 1954. Eighteen patients had chronic lymphocytic leukemia, one giant follicular lymphoma, five lymphocytic lymphosarcoma, and six Hodgkin's disease. The diagnosis in each patient was established by history, physical examination, and hematological studies, usually including bone marrow aspiration. Surgical biopsies of lymph nodes were performed in all patients with lymphomas. Complete blood cell counts and platelet counts were made right before the start of therapy and three times weekly for hospitalized patients and less often for clinic patients. Only in rare instances were bone marrow aspirations repeated. Radiological and other laboratory studies, including hepatic and renal function studies, were performed at appropriate intervals. Following completion of a course of therapy, patients were seen regularly in the outpatient clinic.

Chlorambucil was available in 2 and 10-mg. tablets, which were stored in tightly stoppered brown bottles in a dark, cool place because of chemical instability. Administration was by mouth in all cases. With a standard daily dose of about 0.1 to 0.2 mg. per kilogram of body weight, an average course in most cases consisted of 6 mg. per kilogram. We have usually employed single daily doses of 6 to 10 mg., however, individual doses ranged from 3 to 30 mg., depending on the weight of the patient, diagnosis, hematological picture, and previous therapy. A course of therapy usually lasted five to seven weeks; however, three patients were treated for 14 or more consecutive weeks. The average total dose was 350 mg.; the total effective dose varied widely in different patients, one receiving as little as 50 mg., while some received over 900 mg. The results of therapy in the four groups of patients are summarized in table 1.

Chronic Lymphocytic Leukemia.—Eighteen patients with chronic lymphocytic leukemia were treated with 20 courses of chlorambucil. All patients except one



Structural formulas of the nitrogen mustard methyl-bis (β-chloroethyl)-amine and related compounds, including chlorambucil.

(case 18, table 2) were treated because of symptomatic conditions. Table 2 gives sex and age of patients and duration of disease prior to commencement of the experimental therapy, previous treatment and its effect, pertinent details of chlorambucil dosage with results, and the present status of patients. Objective improvement was rated as "excellent" when the hemoglobin level and white blood cell count returned to normal and when there were significant improvement of the differential count and disappearance of hepatosplenomegaly and lymph node enlargement; as "good" when there were a significant

TABLE 1.—*Results of Therapy with Chlorambucil in Thirty Patients*

Diagnosis	Patients, No.	Objective Improvement: Excellent	Objective Improvement: Good	Objective Improvement: Slight None	Subjective Improvement: Marked or Moderate
Chronic Lymphocytic leukemia	18*	3	8	9	8
Giant follicular lymphoma	1	..	..	1	0
Lymphocytic lymphosarcoma	5	..	2	3	0
Hodgkin's disease	6	..	1	5	1

* 20 courses.

fall in white blood cell count, a slight change in differential count and rise in hemoglobin level, and a decrease in the size of the liver, spleen, and lymph nodes; as "slight" when the white blood cell count fell significantly, there was little improvement in differential count and hemoglobin level, and there was a slight decrease in size of liver, spleen, and lymph nodes; and as "none" when there was no effect. Subjective improvement was rated as "marked" when patients no longer had complaints that they had had on admission and were able to return to their activities with a sustained period of well-being; as "moderate" when they no longer had the complaints and returned to limited activities, and as "none" when there was no effect on their complaints and they were unable to resume activities.

A significant fall in the white blood cell count to less than 30% of initial values was observed in 14 instances. In one patient (case 15), although the white blood cell count fell from 280,000 to 78,000 per cubic millimeter, the blasts, which had at first been 5%, actually increased to 75% on smear. Of the patients in whom there was a fall in white blood cell count, the percentage of lymphocytes was decreased by 25% or more in six instances (cases 2, 4B, 5, 7, 14, and 18). A decrease in hepatosplenomegaly and lymph node enlargement was observed in eight patients. Excellent objective improvement was observed in three instances (cases 4B, 12, and 14), good objective improvement in eight (cases 2, 4A, 5, 6, 7, 8B, 11, and 18), and slight or no objective improvement in the remaining nine cases. Subjective improvement was less regular than objective improvement. More than half the patients who showed objective improvement reported an increase in general well-being and appetite and a decrease in fatigue and ability to return to some normal activities. In 3 instances (cases 7, 12, and 14) marked subjective improvement was reported, while in 5 instances (cases 4A, 4B, 5, 6, and 11) moderate subjective improvement was reported and there was none in 12. The average duration of remission in eight cases (cases 4A, 4B, 5, 7, 8B, 11, 12, and 14) in which the patient responded to therapy and lived more than two months was about five months.

Lymphomas.—Table 3 summarizes pertinent information on 12 patients with various lymphomas. The results in this small series were not as encouraging as in the treatment of chronic lymphocytic leukemia. In a patient with giant follicular lymphoma (case 1, table 3) response to therapy was moderately good, lymphosarcoma showed moderate objective improvement and reported good subjective improvement (cases 4 and 6). One with Hodgkin's disease (case 12) showed temporary marked improvement but failed to respond to a second course of chlorambucil therapy.

TABLE 2.—*Effect of Oral Administration of Chlorambucil on Subacute and Chronic Lymphocytic Leukemia*

						Data Before / After Therapy								
Case	Patient's Sex, Age	Duration Disease Before Chlorambucil Therapy, Yr.	Previous Therapy and Results	Dosage Range Mg. × Days/ Total Dose	Dose in Mg./Kg.	White Blood Cell Count, 10^3	Lymphocytes, %	Hemoglobin Level, Gm./100 Cc.	Platelet Count, 10^3	Liver Size, Cm.	Spleen Size, Cm.	Nodes, 0=4+	Improvement Objective	Improvement Subjective	Duration of Remission and Present Status
1	F 54	2	X-ray—good	6×6/36	0.7	90.0/8.0	90/100	9.2/9.2	....	4/4	4/4	4+/4+	Slight	None	None Died after 1 wk.
2	F 71	Unknown	None	6-8×46/224		267.0/47.5	97/72	10.3/10.5	490/172	0/0	0/0	+/+	Good	None	None Died after 2½ mo. (Parkinson's disease)
3	M 70	2	Triethylene melamine—poor	10×17/170	2.3	214.0/180.0	99/97	9.8/9.8	73 slight decrease	1/1	2/2	3+/3+	Slight	None	None Alive after 3 mo.
4A	F 64	2	X-ray—good Triethylene melamine—poor	10×21/210	3.2	535.0/80.0	97*/98	6.9/10.31	64/62	9/9	12/10	4+/2+	Good	Moderate	6 mo. (See 4B)
B	..	..	Chlorambucil—good	10×91/980	14.3	400.0/14.1	100/78	7.4/12.1	80/78	9/1	10/1	2+/±	Excellent	Moderate	3 mo. (present) Alive after 12 mo.
5	F 77	? 2	None	6-12×50/372	6.8	357.0/8.0	98*/12	10.5/10.8	314/160	6/3	5/5	4+/2+	Good	Moderate	3 mo. Died after 4 mo.
6	M 69	2	Urethan—good Triethylene melamine—good	4-10×62/586		76.8/24.8	97/92	13.6/13.3	62/74	2/2	3/1	2+/+	Good	Moderate	Partial Alive after 4 mo.
7	F 49	1/2	Cortisone—none	2-10×120/588	7.7	490.0/4.9	99/70	4.0/10.7†	28/14	4/1	8/6	4+/3+	Good	None	With steroid maintenance therapy Alive after 14 mo.
8A	M 63	5	Triethylene melamine—good	8-10×24/232		Patient failed to return for follow-up							‡None	‡None	None (See 8B)
B	..	..	Chlorambucil—none	10×15/450	5.6	348.0/19.0	99/80	11.5/12.5	115/74	3/3	5/5	4+/+	Good	Marked	7 mo. Alive after 15 mo.
9	F 67	1	None	10-20×45/560	13.0	333.0/142.5	99/98	3.5/8.8†	130/139	12/12	1/1	4+/4+	None	None	None Alive after 4 mo.
10	M 67	2	X-ray—good	6×3/18	0.3	379.0/339.0	100/100	12.1/12.1	88/76	0/0	0/0	4+/4+	None	None	Died after 5 days (inadequate trial of therapy)
11	M 73	3 days	None	10×71/646	11.0	212.0/30.0	94/86	7.8/10.3	100/90	10/0	9/2	2+/±	Good	Moderate	2 mo. Alive after 3 mo. (present)
12	F 56	4	Triethylene melamine—good	10×92/360	6.0	84.3/14.1	86/58	13.6/13.0	198/170	0/0	2/0	0/0	Excellent	Marked	1 mo. Alive after 3 mo.
13	F 55	2	X-ray—poor	6-10×65/678	12.0	259.0/219.0	97/97	9.5/10.1	128/67	4/4	12/12	3+/3+	None	None	None Alive after 16 mo. (Improved on prednisone therapy)
14	F 59	3/4	None	6-18×42/534	7.8	254.0/8.0	93*/52	12.4/14.5	102/88	10/4	10/3	4+/0	Excellent	Marked	9 mo. Alive after 11 mo.
15	F 65	1/3	Cortisone—poor	6-10×12/116	2.0	280.0/78.5	90*/100	9.5/6.7	143/..	14/14	12/12	3+/3+	None	None	None Died after 2 wk. (subacute lymphocytic leukemia)
16	M 73	3/4	None	6-12×31/250	5.2	219.0/321.0	100/100*	12.4/11.2	.../..	2/2	2/2	2+/2+	None	None	None Alive after 15 mo. (Improved on radiation of spleen)
17	M 57	3	X-ray—good Cortisone—poor	10×15/150	2.5	7.3/2.1	70/62	7.9/9.0	100/70	16/16	20/26	0/0	None	None	None Died after 4 mo.
18	M 71	?	None	5×10/50	1.0	70.0/11.1	93/48	9.7/10.2	242/185	10/10	0/0	+/+	Good	None	None Died after 2 mo. (Parkinson's disease)

* Up to 5% lymphoblasts. † Transfusions required to maintain hemoglobin level. ‡ Spleen extended to iliac crest.

but only when steroid therapy was also given. However, she had severe agranulocytosis and thrombocytopenia with pneumonia and purpura when chlorambucil was administered, although only a very small total dose was used (2.3 mg. per kilogram of body weight). Two patients with lymphocytic

Toxicity.—The drug was administered orally and produced no gastrointestinal side-effects. There were no instances of hepatic or renal complications. Toxic effects in the bone marrow to the extent of moderate leukopenia were actually desirable, and in patients with lymphomas were used as an index of sufficient

therapy. On the other hand, severe leukopenia and thrombocytopenia did occur in one patient who had giant follicular lymphoma and who had been treated with radiotherapy, even though she received a relatively small dose of chlorambucil (case 1, table 3). In another patient, a man with chronic lymphocytic leukemia (case 8B, table 2), administration of chlorambucil brought about such a rapid decrease in the number of lymphocytes that hyperuricemia resulted. The patient drank an insufficient amount of water during hard manual labor on a very hot day, which resulted in dehydration, oliguria, and, subsequently, transient anuria that was shown to be due to formation of uric acid crystals. The patient recovered after a stormy course and his condition is now in remission.

Autopsies.—Of the 30 patients treated, 10 have died and autopsies have been performed on 5 (cases 1 and 15, table 2; cases 2, 4, and 10, table 3). In findings of all autopsies, there was evidence of active disease with involvement of lymph nodes, viscera, and other organs. On microscopic examination, characteristic neoplastic cells were easily recognized and no evidence of cytotoxicity was described. Gross examination as well as microscopic study showed no evidence of hepatic or renal disease that could be attributed to drug toxicity. Hypoplastic marrow was described in three instances, but in two cases there was diffuse replacement by tumor tissue.

TABLE 3.—*Effect of Oral Administration of Chlorambucil on Lymphomas*

Case	Patient's Sex, Age/Yr.	Duration Disease Before Chlorambucil Therapy, Yr.	Previous Therapy and Results	Dosage Range Mg. × Days—Total Dose	Dose in Mg./Kg.	Data Before / After Therapy: White Blood Cell and/or Platelet Count Lowered by Therapy	Hemoglobin Level Gm./100 Cc.	Liver, Size, Cm.	Spleen, Size, Cm.	Nodes 0=4+	Duration of Remission and Present Status
Giant Follicular Lymphoma with Marked Lymphocytosis											
1	F 42	3	X-ray—good	100/14.140	2.3	Yes*	8.5/8.0†	8/3	10/2	4+/1+	† Chlorambucil induced remission Alive after 10 mo.
Lymphocytic Lymphosarcoma											
2	F 66	1	Triethylene melamine—good	6-30/46/528	14.5	Yes	8.0/10.3	2/3	0/2	3+/2+	None Dead after 1½ mo.
3	M 65	1½	Triethylene melamine—good	6/17/102	1.6	?	?	?	?	?	Dead after 3 mo.
4	M 55		X-ray—good	6-10/53/438	7.4	Yes	12.6/10.0 White blood cells, 65,000 → 3,200 Lymphocytes, 90% → 23%	2/0	0/0	3+/+	Partial Alive after 2 mo.
5	M 58	2	X-ray—fair	9/4/11/264	4.0	Yes	13.1/10.7	../..	../..	../..	None Died after 8 mo. (improved temporarily on prednisone therapy)
6	M 42	8 wk.	None	10/8/8/80	13.0	Yes (temporarily)	10.2/12.4	4/3	3/1	4+ large abdominal mass/2+ smaller abdominal mass	Partial Alive after 4 mo.
Hodgkin's Disease											
7	F 26	2	HN2 and X-ray—good Cortic-tropin, cortisone—poor	6/6/4/384	6.3	Yes	11.5/11.5	0/0	0/0	3+/3+	None Died after 3 mo.
8	F 40	3	X-ray—fair	10-8/0/42/320	9.0	Yes	8.8/9.0	0/0	0/0	Mediastinal/ No change	None Alive after 6 mo. (slight improvement on triethylenethiophosphoramide therapy)
9	F 23	24	HN2—fair Steroids—none	10/4/1/430	7.0	Yes	9.9/11.9‡	0/0	1/1	0/0	None Alive after 6 mo.
10	M 34	5	X-ray—good HN2—poor	10-30/0/21/420	6.2	Yes	11.2/12.4	2/2	1/1	4+/4+	None Dead after 1½ mo.
11	F 23	6	X-ray—good HN2 and triethylene melamine—fair	10/6/60	1.7	Yes	6.7/11.5‡	0/0	5/5	0/0	None Dead after 5 mo.
12A	F 27	6	X-ray—good HN2, triethylene melamine, steroids—fair	6-16/0/48/490	8.9	Yes	12.1/12.0	0/0	0/0	4+/±	2 mo. See 12B
B		..	Chlorambucil—good	10/0/36/360	10.0	Yes	10.6/10.5	0/0	0/0	3+/3+	None Alive after 8 mo.

* Severe agranulocytosis and thrombocytopenia with pneumonia and purpura followed by complete recovery.
‡ Transfusions required to maintain hemoglobin level.

Comment

Galton and others [6] reported recently on their experience with chlorambucil. They treated 62 patients suffering from malignant lymphomas with a dosage schedule similar to that used in our study. They obtained excellent remissions in 4 of 23 patients with Hodgkin's disease, in 7 of 12 patients with lymphocytic lymphoma, in 4 of 8 with chronic lymphocytic leukemia, and 5 of 6 with follicular lymphoma. They

noted that side-effects were fewer than those noted in therapy with nitrogen mustard or triethylene melamine (TEM), and they felt that profound marrow depression was directly related to the dosage and was therefore avoidable. Prossor and co-workers [7] of the Westminster Hospital in London employed chlorambucil in a total of 39 cases, including 24 of Hodgkin's disease, 2 of lymphosarcoma, 3 of lymphocytic leukemia, 2 of granulocytic leukemia, 4 of plasma cell myeloma, and 3 of generalized carcinomatosis. It was the feeling of the authors that "good temporary palliation" was achieved in a good proportion of patients, particularly those with lymphoma. No further details are given in this preliminary report.

It is our impression that chlorambucil is of beneficial effect in certain patients with chronic lymphocytic leukemia. Decreases in the white blood cell count, some reversal of the differential count, improvement of hemoglobin level, and some decrease in hepatosplenomegaly and lymph node enlargement can be expected in about two-thirds of the cases. This coincides with improvement in the well-being of the patient in about one-half of the cases.

A comparison of results in this series with those obtained by other modes of therapy is difficult. It has been stated repeatedly that radiotherapy decreases morbidity in chronic lymphocytic leukemia with no effect on survival time. Most statistical analyses, however, do not deal with remission rate and duration of remissions. An analysis of the duration of remission with techniques of titrated total body radiation by external x-ray [8] or radiophosphorus (P^{32}) [8b] is impossible, because repeated small doses are administered to keep the patient in constant remission. In chronic lymphocytic leukemia, use of urethan reduces the abnormal blood cell count, but maintenance therapy is necessary, and when administration is discontinued the count rises promptly.[9] In some cases, remissions of three and one-half to six months have been observed.[10]

Triethylene melamine is useful in chronic lymphocytic leukemia since small doses produce improvement lasting three to five months,[11] but rarely longer.[12] Triethylene melamine therapy may, however, be hazardous, particularly in patients with low platelet counts.[11] With chlorambucil therapy, remissions of three to six months may occur in the conditions of those patients who respond.

In those patients in whom thrombocytopenia is an initial finding, chlorambucil appears to be of particular usefulness. Galton [6] has pointed out that depression in platelet level is rarely serious. In the present series of patients with chronic lymphocytic leukemia, half had initial platelet counts below 100,000 per cubic millimeter, although none had overt hemorrhagic phenomena. With effective courses of chlorambucil therapy, the platelet levels did not fall significantly in any of these patients.

The wide range of doses required by different patients is of interest. Of the nine patients who had chronic lymphocytic leukemia and who did not respond, two patients showed no significant response after the administration of 12 and 13 mg. per kilogram of body weight of chlorambucil given over 65 and 45 days respectively. On the other hand, in certain patients a marked fall in white blood cell counts occurred with doses of as little as 0.7 and 1 mg. per kilogram of body weight given over 6 and 10 days respectively. The cause for this variability in response to therapy is not clear. It may be due to differences in gastric acidity, absorption, or utilization. The two patients showing no response to large doses of chlorambucil had moderately low gastric acidity. The period of therapy required with chlorambucil is considerably longer than with triethylene melamine. Thus, in one patient, the administration of single doses of triethylene melamine resulted in remissions of one year on two occasions. In contrast, therapy with chlorambucil required nearly two months to induce a similar response in the same patient.

Our experience with chlorambucil therapy in the other lymphomas has not been extensive. Patients with lymphocytic lymphosarcoma appear to respond less well than those with chronic lymphocytic leukemia. The response to this therapy in patients with Hodgkin's disease is not as good as to therapy with methylbis (β-chloroethyl)-amine or triethylene melamine, although we have observed one patient in whom significant improvement occurred with chlorambucil therapy after resistance to other nitrogen mustards had developed. These results are similar to those reported in the larger series of Galton.[6]

Summary

Thirty patients were treated with chlorambucil [*p*-(di-2-chloroethyl)aminophenylbutyric acid] (CB 1348), an aromatic nitrogen mustard. Satisfactory responses were obtained in patients with chronic lymphocytic leukemia; the drug appears to be of particular usefulness when patients with this disease also have moderate thrombocytopenia. Chlorambucil was found to be of less value in lymphocytic lymphosarcoma and Hodgkin's disease. We have found the drug to be relatively free of side-effects when administered orally. Effective therapeutic doses cause bone marrow damage only rarely.

630 W. 168th St. (32) (Dr. Ultmann).

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HIATAL HERNIA COMPLEX

HIATAL HERNIA, PEPTIC ESOPHAGITIS, MALLORY-WEISS SYNDROME, HEMORRHAGE AND ANEMIA, AND MARGINAL ESOPHAGOGASTRIC ULCER

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• *The junction of the esophagus and stomach is normally closed except during deglutition, but the structures and mechanics involved in the closure are poorly understood. Roentgenologic observations indicate that the lowermost segment of the esophagus, over a length of 2 to 4 cm., constitutes a functional internal sphincter and that the muscle bundles about the hiatus of the diaphragm constitute an external sphincter.*

Dislocation of these sphincters in the presence of a hiatal hernia may disturb the closing mechanism at the cardia and permit reflux of gastric juice into the esophagus. The ensuing peptic esophagitis causes most of the symptoms usually ascribed to the hiatal hernia. Further complications are acute lacerations at the esophagogastric junction with severe hemorrhage following vomiting, the peptic marginal ulcer sometimes converted from these lacerations by chronic peptic irritation, and slowly developing anemia. The close interrelation of these conditions to each other and to the disturbed sphincteric closure in the presence of a hiatal hernia is illustrated by roentgen observations, diagrams, and a report on a patient with fatal Mallory-Weiss lacerations.

Although large hiatal hernias had been observed earlier, small and medium-sized hiatal hernias became recognized with increasing frequency in the 1920's. To Carman and Fineman [1] in the United States and to Åkerlund [2] in Stockholm goes the credit for having brought the hiatal hernia to our clinical awareness. Harrington,[3] Reich,[4] Anders,[5] and others have contributed much to our knowledge of anatomy and physiology of the cardia. The "epiphrenal syndrome" was described by von Bergmann, and the association of hiatal hernia and anemia was also early pointed out by Ohnell. "Peptic esophagitis" was another new concept. Earlier observations in the esophagus, made at autopsy, had been interpreted as postmortem digestion by regurgitated gastric juice. Hamperl [6] described the gross and microscopic pathological features of peptic esophagitis as recently as 1934, and Winkelstein [6] in 1935 independently reported "Peptic Esophagitis: A New Clinical Entity." Subsequent contributions have come from Allison, Johnstone,[7] and Barrett,[8] in England. Mallory and Weiss [9] observed longitudinal lacerations at the cardia in patients who died of upper gastrointestinal hemorrhage. Gastric resection may control massive upper gastrointestinal bleeding of unknown origin.

Most of these observations are rather new, and some of them seem quite unrelated. An attempt will be made here to correlate them and to establish their clinical significance. It appears advisable to commence with a brief discussion of the anatomy and physiology of the cardia as I see them, since there is no full agreement on this subject. The difficulties are increased by a confusing nomenclature. My concept is based on the literature, my own observations, and joint observations with colleagues in pathology and surgery.

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Location of the Cardia

The tubular gullet enters the bag-like stomach at a point that is marked, at the greater curvature, by a fairly constant indentation, the incisura cardiaca. There is no corresponding landmark at the lesser curvature or the inner mucosal surface. The opening

of the funneling lower end of the tube is called the cardiac opening or anatomic cardia. The funnel-shaped structure extending from the diaphragm to the cardiac opening has always been called the abdominal portion of the esophagus, and the functional separation of esophagus and stomach has been placed at the cardiac opening. Many observations of the past 30 years, however, make this concept untenable. No in-

Fig. 1.—"Cardiac antrum of stomach." Two examples of stomachs (roentgenograms taken with patients in prone position but turned so that reader faces patient) in which barium-air contrast offers clear view of "abdominal portion of esophagus." In these instances this tubular or conical portion is lined by mucosa presenting the convoluted gastric rugal pattern, and the visible occlusion is at the level of the diaphragm rather than at the anatomic cardia, identified by the incisura cardiaca.

trinsic occlusive mechanism has ever been observed at the anatomic cardia. Some authors believe that the oblique implantation of the tubular structure into the stomach provides a flap with a valve-like action. The roentgenologic morphology of this "cardiac valve" has been thoroughly explored by Jutras, Levrier, and Longtin. Neither roentgenologic nor esophagoscopic observation has demonstrated any occluding mechanism at this level. The great variability in the mode of formation and depth of the incisura cardiaca also militates against this hypothesis.

Reich's [4] work in 1927 with use of wax casts of the stomach provided one of the earliest hints that the physiological cardia, the functional occlusion between esophagus and stomach, might lie at the level of the diaphragm. Many other data point in this direction. Only the simplest roentgenologic observations shall be mentioned here. If we observe the swallowing act, with the subject in recumbent position, we may see the bolus pass down and come to a temporary stop just above the diaphragm. Then something opens and the barium slides down into the stomach. If we make the patient take a deep breath while the barium is just passing through, the barium column is broken by a wide band-like interruption that keeps the upper segment arrested for the time the inspiratory standstill is maintained. As soon as the diaphragm is relaxed, the barium resumes its flow in full width through the reopened straits. The level of this complete closure on deep inspiration is the same as that of the temporary stop or the slight narrowing of the barium shadow observed during quiet respiration. In addition to the known relation of onset of the swallowing act and respiration, there is also a well-harmonized interplay of the normal respiratory movement of the diaphragm and the activity of the lower portion of the esophagus and functional cardia. Of several related facts in the area of pathology, only the case of cardiospasm or achalasia of the esophagus may be mentioned here. The obstructing narrowing in this condition is always seen at the level of the esophageal hiatus of the diaphragm or above it, but never at the anatomic cardia.

Abdominal Portion of the Esophagus

The transition from the stratified squamous epithelium of the esophagus to the columnar gastric epithelium has been thought to occur at the anatomic cardia. In reality it is found somewhere between the level of the diaphragm and the cardiac opening. Furthermore, instead of a smooth circumferential line, this transition often consists of finger-like extensions of both mucosal structures interlacing with each other for a considerable distance. The funnel-shaped dilatation of the "esophagus" after its passage through the diaphragm may be lined wholly or in large part by gastric epithelium with cardiac glands. With the oc-

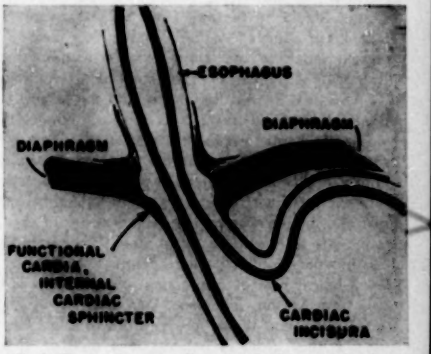

Fig. 2.—Diagram of normal cardiac region. Esophagus is anchored to rim of esophageal hiatus of diaphragm by fibers of phrenoesophageal ligament. Incisura cardiaca *(right lower arrow)* indicates site of "anatomic cardia." Diaphragm forms external sphincter of "functional cardia" *(left lower arrow)*. Internal cardiac sphincter (see text) is indicated by the diagramatically exaggerated swelling of muscularis propria of esophagus. Variable zone of transition from esophageal to gastric mucosa is kept black.

cluding mechanism between esophagus and stomach established at the level of the diaphragm, it seems reasonable to call the subdiaphragmatic part the cardiac antrum of the stomach, rather than the abdominal portion of the esophagus. Embryologic data also support this view.

Roentgenologic observations conform with this new concept much better than with the traditional one.

Whenever a subdiaphragmatic funnel-shaped structure can be visualized—this is rarely possible with a completely distended fundus—the lining mucosa usually presents a rugal pattern similar to that of the stomach rather than to that of the esophagus (fig. 1). The incisura cardiaca, marking the cardiac opening, is formed by the oblique fibers separated from the circular fibers in the muscular coat of the stomach. The depth of the incisura cardiaca varies from subject to subject and undergoes functional changes in a single individual. If the stomach is dilated, the incisura is blunted and may completely disappear, and the so-called abdominal portion of the esophagus becomes absorbed by the stomach (Palmer [10]). This brief discussion may be concluded with Allison's statement based on esophagoscopic observation that there is in the normal subject "in life no such thing as the abdominal esophagus" (fig. 2).

Functional (or Physiological) Cardia

I recommend application of the term functional cardia as opposed to the "anatomic cardia" of old tradition. One may use the term esophagogastric mucosal junction for the transition of the two types of

Fig. 3.—Coronal, longitudinal section through lower portion of esophagus, cardia, and diaphragm with explanatory diagram (from holoptic section). Stumps of diaphragm embrace intestine on either side. Transition from slender longitudinal mucosal folds of esophagus to thicker convoluted gastric folds at hiatal level is clearly seen. Circular and longitudinal layers of muscularis propria of esophagus are becoming slightly thicker at and below hiatus (from Reich, L.: Antrum Cardiacum, Incisura Cardiaca und Gashlase des Magens, *Fortschr. a. d. Geb. d. Röntgenstrahlen [Tagungsheft.]* **50**: 37, 1937).

epithelium. Unfortunately, the abbreviated term esophagogastric junction has been used alternately for both the epithelial transition and the closing mechanism, without any explanation or definition, as if the epithelial transition was necessarily located at, or had anything to do with, the functional closure.

The circular layer of the muscularis propria of the esophagus is rather strong in the lowermost portion. Most anatomists do not find a morphologically identifiable ring-shaped sphincter (some mammals, e. g., the porpoise, have a quick-acting cardiac sphincter); Laimer and Lerche are exceptions. There is general agreement, however, that the lowermost portion of the esophagus, called vestibule by some, has a sphincteric capacity over a length of 2 to 4 cm., and it is practical to call this the "internal sphincter" of the physiological cardia. Very little has been written in regard to the longitudinal muscle, although it plays an integral part in the transport of ingesta in any hollow viscus. In particular, contraction of the longitudinal muscle acts to pull up the cardiac end of the stomach. There is good reason to assume that the mucous membrane also plays a part, both passively, by heaping up during narrowing of the lumen, and actively, by the controlling muscularis mucosae. Hardly any controversy exists about the "external sphincter" provided by the diaphragmatic muscle bundles that form the hiatus, the "pinchcock action" of the diaphragm (Jackson; Reich [4]) (fig. 3).

Esophageal Hiatus

The esophageal hiatus of the diaphragm is formed in man by fasciculi of the right crus; only rarely do bundles of the left crus cross to take part in it. Fibers of the fascia from the undersurface of the diaphragm and probably also some muscular fibers of the diaphragm merge with the muscular tube of the esophagus in a funnel-like fashion to form the phrenoesophageal ligament, which anchors the esophagus to the rim of the hiatus. The suspension of the esophagus within the hiatal ring of the diaphragm provides for rather wide lengthwise movements of the esophagus. We make ample use of this movability during breathing, during filling and emptying of the stomach, and in changing from supine to erect position. This flexibility is the main reason why it is so difficult to establish the topographic relations at the esophageal hiatus by the routine method of postmortem dissection and why it is often difficult or impossible at death to establish the antemortem presence of a small or medium-sized nonincarcerated hiatal hernia. Excursions of the esophagus may become excessive in abnormal conditions: severe cicatricial esophagitis or a posterior mediastinal tumor may pull the functional cardia and a portion of the stomach upward; pneumoperitoneum in the erect position allows liver, spleen, and stomach to fall away from the diaphragm, pulling a sizable portion of the esophagus down into the abdomen, to slip back when the subject lies down.

In addition to the up and down movement of the esophagus as a whole, in relation to the diaphragm, or of the diaphragm in relation to the esophagus, the mucosal tube moves within the muscular tube of the esophagus. This motion was suggested early by fluoroscopic observations (Reich [4]) and has been confirmed and amplified by Allison's roentgenologic observations of silver clips implanted through the esophagoscope in the mucous membrane at the esophagogastric epithelial transition. Additional information has been obtained in the experimental animal by observing metal balls attached to the outside of the esophagus (Nauta [11]) and by endoscopy through a gastrostomy.

The loose submucosa permits considerable up and down movement of the mucous membrane within the muscular tube of the esophagus. Spontaneous up and down migration of limited amplitude occurs in the resting organ, presumably controlled by longitudinal contractions of the muscularis mucosae. During deglutition the mucosa moves upward to meet the bolus, receives it, carries it down, and while ejecting it everts into the stomach, forming a rosette-like protrusion (comparable with visible movements of the anus of a defecating horse) (Nauta [11]). This is sometimes seen as a lobulated soft tissue mass protruding into the right upper corner of the gas-filled fundus. A small pocket of gastric mucosa quite commonly appears above the diaphragm while the bolus passes, to disappear immediately afterward (Palmer [10]).

With this wide range of normal change in position, it would be arbitrary and probably incorrect to state that a certain level of the esophagus or mucous membrane is normally situated at the level of the diaphragm. Furthermore, the transition from the normal condition to a hiatal hernia is obviously gradual. With

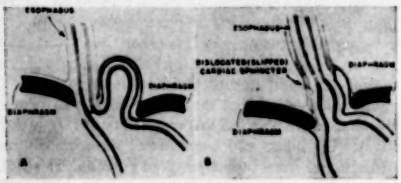

Fig. 4.—A, paraesophageal, or rolling hiatal, hernia. Esophagus is assumed to be fixed at right (posterior) portion of hiatus, while fundus of stomach has herniated along it through widened hiatus. *B*, axial, concentric, or sliding hiatal hernia. Esophageal hiatus is usually widened. Esophagus and adjacent portion of stomach have slipped upward, resulting in local dissociation of the internal (esophageal) and external (diaphragmatic) cardiac sphincter. Esophagus usually is shortened and contracted, but sometimes is of normal length and tortuous. A peritoneal hernial sack surrounds herniated stomach only partially, according to most authors—therefore, sliding hiatal hernia. Dislocated internal cardiac sphincter *(arrow)* deprived of support by its external partner, the diaphragm, often becomes incompetent.

such fluctuations in function and time, the extreme reluctance of some to diagnose a small hiatal hernia and the criticism of others that hernias are diagnosed too often lose their meaning. A small hiatal hernia is frequently a physiological borderline situation without clinical significance; it may, however, have the inherent potentiality of becoming larger and significant.

Hiatal Hernia

Among the factors responsible for the formation of a hiatal hernia, only those that bear on the problems under discussion here will be briefly listed. The width of the esophageal hiatus varies greatly in normal conditions. Harrington examined the hiatus during 1,000 consecutive laparotomies. In 55% the hiatal rim surrounded the esophagus tightly; in 35% one finger could be inserted between the esophagus and the margin of the hiatus; and in 10% two or three fingers could be inserted. The hiatus seems to become wider with increasing age. As at any other site of abdominal hernias, an increased width of the opening is not in itself pathological; however, it favors herniation. The hiatal opening is always found wider than normal when hiatal hernias have formed.

Individual variations in strength and tightness of the phrenoesophageal ligament may well be assumed. The suspensory apparatus loosens in the course of debilitating disease and advancing age. Increased abdominal pressure plays a role as in other hernias. Transient or persisting hiatal hernia occurs in the presence of ascites, large abdominal tumors, late pregnancy, and experimentally increased intra-abdominal pressure. Vomiting and abdominal injury with bracing of the trunk may induce hiatal hernia by sudden increase of the intra-abdominal pressure in predisposed subjects.

If one omits, for the purposes of this discussion, large hernias where the greater part of the stomach lies in the chest and considers only small and medium-sized hernias, one usually distinguishes two types: (1) those in which the esophagus and stomach have slipped through the hiatus as a whole in an axial fashion, therefore axial or concentric hernia or, because of the incomplete peritoneal investment, sliding hernia, and (2) those in which the fundus of the stomach seems to have slipped upward along the esophagus, therefore paraesophageal or rolling hernia (parahiatal hernia [Sweet]). The slipping up and down, however, with change of position or degree of filling, is not designated by the term sliding hernia referred to in the first type. The surgical term, sliding hernia, generally indicates a hernia where the herniated viscus is invested by peritoneum only for a portion of its circumference. This is the case in many axial hernias; it is not clear, however, whether this is the rule in all cases (Allison; Harrington). While this feature is important for the surgical handling of a given case, it cannot be predicted in detail. It is, therefore, preferable to designate these hernias with the unassuming descriptive term "axial or concentric hernia" in logical antithesis to the paraesophageal type. In both types one can usually recognize the dislocated internal cardiac sphincter (fig. 4). Both types may be spontaneously reducible or permanently incarcerated. A small or medium-sized hernia visible in recumbent position may change its size considerably or disappear in the erect position.

In the paraesophageal hernia the anchorage of the esophagus to the right and posterior portion of the hiatal ring appears to be more secure in many individuals than at the remainder of its circumference. An outpouching of the diaphragmatic peritoneum between esophagus and hiatal rim is believed to precede the prolapse of a portion of the gastric fundus. Vestigial peritoneal clefts may play a role in certain instances. These hernias, except for their esophageal part, are usually completely covered by peritoneum.

The characteristic indentation between esophagus and herniated gastric pouch, in my opinion, represents the persistent incisura cardiaca, a structural feature of the stomach, not a fasciculus of diaphragmatic muscle (Sweet). In the paraesophageal hernia the incisura cardiaca is preserved; in the axial type it is effaced. Occasionally the same small hernia may seem axial in type with a low esophageal ring when filled, distended, and spot-filmed during inspiration, while it appears paraesophageal with marked indentation when roentgenographed fairly empty, collapsed, during expiration.

In both types of hernias a circular narrowing 2 cm. or more above the diaphragm is usually seen. This irregular narrowing changes in width and may disappear when the esophagus widens during the passage of barium, to reappear at the same place when the bolus has passed. The mucosa below this narrowing usually has the pattern of gastric folds. On roentgenologic and gastroscopic evidence this circular narrowing represents the dislocated internal sphincter of the functional cardia. This slipped cardiac sphincter is often continent under otherwise normal conditions. This weak sphincter, however, deprived by its dislocation of the support of the external sphincter, easily becomes incompetent, permitting reflux of gastric content into the esophagus. In rare instances the slipped sphincter becomes spastic and causes dysphagia. The "lower esophageal ring" of Schatzki and Gary,[12] and Ingelfinger and Kramer,[13] is caused, in my opinion, by sphincteric action of the muscularis mucosae at the level of the slipped internal sphincter in response to superficial ulceration there, thus elevating and molding this diaphragm-like mucosal fold. In the irreversible case it soon develops into submucosal inflammation and a submucosal fibrotic ring, resembling the fixed diaphragm-like mucosal fold encountered with peptic ulcers in the gastric antrum.

Peptic Esophagitis

The discussion of peptic esophagitis in this context, as well as the discussion on marginal ulcer in a later section, is necessarily aphoristically brief. The reader is referred for comprehensive information to Palmer, Schmidt, and Barrett.

Heartburn has been believed for a long time to be caused by reflux of acid gastric contents into the esophagus. However, this was considered rather a layman's interpretation, and scientific medicine expressed itself very cautiously on this subject. The clinical symptoms of hiatal hernia have been explained, until very recently, in various ways, often without proper consideration of reflux of gastric juice and peptic esophagitis. While Robins and Jankelson observed gastroesophageal reflux first in 1926, Winkelstein,[6] Allison and Johnstone, and Barrett have established the fact of rather frequent reflux of gastric content into the esophagus in the presence of a hiatal hernia and have convincingly demonstrated that the consequent peptic esophagitis is the source of most clinical symptoms. Guided independently by similar considerations for many years, I have been carefully watching the presence or absence of gastric reflux in every instance of hiatal hernia and am convinced of the overwhelming role of peptic irritation of the esophageal mucosa. It must be noted, however, that some authors do not accept this view.

Our knowledge of peptic esophagitis is a recent acquisition. The pathologists, overcautiously, had interpreted the changes found in the esophagus as postmortem digestion caused by regurgitant gastric juice. Though the chronic peptic ulcer of the lower portion of the esophagus had been recognized for a long time, the first modern pathological description of peptic (erosive) esophagitis was published by Hamperl[5] in 1934. The welling up of gastric juice above the slipped

Fig. 5.—Roentgenograms of woman, aged 69, with clinical evidence of rather severe peptic esophagitis. Small, axial hiatal hernia with reflux of gastric content into esophagus, in recumbent position. *A*, small hernia, partially filled with barium. At upper end of this gastric pouch is site of slipped internal cardiac sphincter; above this is slightly irregular mucosal relief of lower portion of esophagus—esophagitis. *B*, spontaneous reflux of gastric content (barium) into esophagus.

cardiac sphincter can be readily seen by esophagoscopy; general inflammation and longitudinal superficial ulcerations are regular findings in instances of symptomatic hiatal hernia (Schmidt; Barrett; Benedict). The roentgenologic observations closely parallel this experience. With small and medium-sized hernias (while examining the subject in recumbent position, the best position being prone with the left side elevated or supine with the right side elevated) we may observe that barium flows back from the stomach into the esophagus. Filling of a herniated pouch in itself does not constitute abnormal reflux. Only backflow into the esophagus reveals incompetence of the sphincter and abnormal reflux. With marked incompetency of the slipped internal sphincter, this reflux can be observed quite regularly. In other cases one may observe it only once or twice during an examination. Competency and incompetency of the sphincter are functional conditions that may change in degree from time to time.

The fact that regurgitation of gastric juice is not necessarily a constant phenomenon is best illustrated by an observation of Johnstone. A woman of middle age had a classic history of peptic esophagitis. At the first roentgenologic examination, a hiatal hernia with reflux was found. At a second and third examination they could not be seen. When the patient reported that symptoms were worst when she was tired, another examination was carried out in the evening, after a full day's work. This conclusively showed a small hiatal hernia and free reflux, which finding was confirmed at operation a few days later. The explanation apparently lies in disturbed coordination and in muscular fatigue.

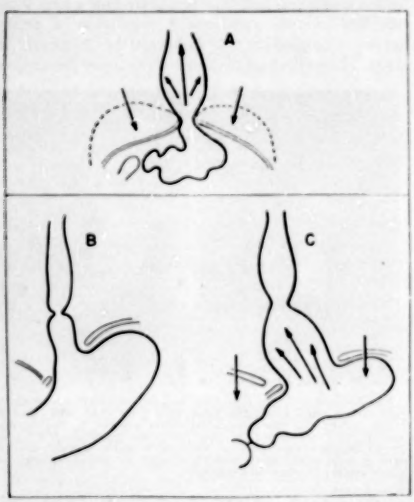

Fig. 8.—A, diagram to explain interaction of forces leading to spontaneous rupture of esophagus by vehement vomiting (after S. A. Mackler[28]). *B*, tracing of roentgenogram of an axial hernia. C, my concept of how, in the presence of such a hernia, interaction of anatomic conditions and forces during vomiting may cause mucosal laceration or complete rupture of esophageal wall (see text).

While gastric reflux usually occurs when the patient is in the recumbent position or stooping over and is of moderate degree, there are a few instances where the patient reports a sudden choking sensation. Here one may observe that, with a sudden inspiratory or expiratory movement of the diaphragm, a large amount of fluid is ejected into the widening esophagus. These patients have completely lost the sphincteric control at the esophagogastric junction.

As with peptic ulceration in general, the severity of peptic esophagitis in a given case is not solely dictated by the strength of the gastric juice and the frequency of its backflow but is also determined by the protective mechanisms of the body, the lack of which is usually described as "ulcer diathesis." In this connection, it may be noted that many instances of peptic esophagitis are associated with duodenal ulcer, suggesting that, with the accompanying hyperacidity, the regurgitant gastric juice becomes more injurious to the esophageal mucosa or that both the duodenal ulcer and peptic esophagitis are coordinated manifestations of an ulcer diathesis. Every bearer of a hiatal hernia is a potential candidate for gastric reflux and peptic esophagitis. I have observed gross reflux only rarely in the absence of a hiatal hernia.

In the newborn infant, incompetence of the physiological cardia is not uncommon; it is known as chalasia of the cardia (Neuhauser and Berenberg[14]). Apparently not all children are born with full mastery of the complicated coordination that makes for control of the cardia. Hiatal hernias, even of considerable size, have been observed in infants (Neuhauser; Silverman[15]). It seems to me that the persistence of these long tubular hernias, acquired in infancy, is the substratum of the baffling condition called by some "esophagus lined by gastric mucosa" (Allison).

The roentgenologic observation of gastric reflux reveals incompetence of the cardiac sphincter mechanism and potential irritation of the esophageal mucosa (fig. 5). Superficial irritation of the esophageal mucosa usually does not manifest itself roentgenologically. In more advanced instances of esophagitis, however, mucosal swelling and ulcerations become obvious. Minor and major irregularities, widening of folds and irregular contours, are seen instead of the perfectly parallel longitudinal folds of the normal esophagus. Only in very rare instances have I found it difficult to distinguish these irregularities of severe esophagitis from the pattern of esophageal varices.

Severe esophagitis with extensive ulceration, deep fibrosis, and muscular hypertrophy leads to extensive stricture and lengthwise shrinking of the esophagus. Etiological factors other than hiatal hernia may contribute, i. e., operations under general anesthesia, debilitating disease, extended forced bed rest, the extended use of a gastric tube, chronic severe vomiting, the early and late stages of pregnancy, and delivery.

It appears that fair agreement has been reached in the last few years concerning the features and theories of the hiatal hernia complex discussed so far. The situation, however, becomes more controversial and even enigmatic when we approach the chronic peptic ulcer or marginal ulcer of the esophagus, hemorrhage and anemia associated with hiatal hernia, and the Mallory-Weiss syndrome.

Mallory-Weiss Syndrome

Mallory and Weiss[9] observed longitudinal mucosal lacerations in the cardiac portion of the stomach at autopsy in patients with fatal hemorrhage and incriminated the preceding retching and vomiting as the main causative factor. Among the first reported cases, alcoholism was prevalent; in a later series, however, this was not the case, and the authors consid-

ered alcoholism merely as a factor initiating gastritis and vomiting. In three of the four cases of the first series, the mucosal tears were limited to the gastric side, extending close to the border of the esophagus; only in the fourth instance did the upper quarter of the tear extend into the esophagus. In the later series the tears appear to straddle the esophagogastric mucosal junction fairly evenly. Mallory and Weiss con-

Fig. 7.—Emergency examination of esophagus and stomach of severely bleeding patient in supine position (case report). Medium-sized hiatal hernia, wide esophageal hiatus, and massive flow of barium from esophagus to stomach and from stomach to esophagus were observed. Lower arrow points to widened esophageal hiatus of diaphragm; upper arrow, to patulous slipped internal cardiac sphincter in a moment of massive gastroesophageal reflux.

cluded from the large number of patients with the identical clinical syndrome who recovered spontaneously that some of these lesions must have a strong tendency to heal. However, they also considered the possibility that the lacerations might lead to chronic peptic ulcers in some instances.

While the pathological findings and clinical coordination with vomiting in this syndrome are well understood, difficulties still exist in visualizing the pathomechanics of the process. These difficulties are analogous to those encountered with the explanation of spontaneous rupture of the esophagus. In order to explain the situation, a diagram adapted from Mackler's [16] study of spontaneous rupture of the esophagus may be used (fig. 6).

Vomiting is understood to consist of a succession of coordinated events: inspiratory standstill, contraction of the gastric antrum forcing its contents toward the fundus, contraction of the abdominal muscles and diaphragm, and ejection of gastric content through the relaxed cardiac sphincter. From fluoroscopy and cineroentgenographic recordings, we are familiar with the ballooning of the lowermost portion of the esophagus during the act of vomiting. One may wonder, however, how a sufficient pressure can be built up to tear the lower portion of the esophagus in the absence of an additional obstruction in the upper portion. The esophagus is filled during the act of vomiting through the relatively narrow cardia, and the tear of spontaneous rupture is always found in the lowermost portion of the esophagus, sometimes extending below the hiatal ring. In complete ruptures the gross distortion of the tissues found at operation or autopsy interferes with detailed study of mode and site of origin. It is reasonable to consider Mallory-Weiss lacerations as incomplete ruptures of the esophageal wall, extending through mucosa and submucosa. If one applies Mackler's diagram to Mallory-Weiss lacerations, it is difficult to understand why a tear should occur in the cardiac portion of the stomach while the stomach is protected against overdistention by the elevated surrounding abdominal pressure. These difficulties, however, may be resolved if we follow the events during vomiting in the presence of a hiatal hernia.

First, the esophageal hiatus is usually wide whenever a hernia exists. Thus, the force of the jet of the ejected gastric contents would not be broken at the hiatal level, as it would in the presence of a competent hiatal ring. Second, the herniated gastric pouch is surrounded by the low thoracic pressure. Against this, the combined pressures of the gastric convulsion and the forceful contractions of the diaphragm and ab-

Fig. 8.—Postmortem specimen of the esophagogastric junction and explanatory diagram (patient in case report). There are four deep longitudinal lacerations of mucosa. Counting from left, (1) and (3) are very recent (microscopically) and (2) and (4) slightly older. From (2) a longitudinal recent scar extends into esophagus for about 2 cm., ending in a shallow ulcer. Four other small round ulcers are at about the same level in esophagus. Arrows indicate esophagogastric mucosal junction.

dominal muscles operate from the inside. Third, the slipped internal cardiac sphincter forms a strait above the hernia, thus adding to the building up of pressure within the hernia. Fourth, the slipped internal sphincter is a natural narrowing of the tube, and, removed from its normally protecting hiatal ring, it is vulnerable to vehement, sudden distention.

Although a recent editorial states that "the question of why the normal esophagus ruptures has not been definitely elucidated," the reasoning above and the following observation, one of several similar ones, may remove these difficulties.

Report of a Case

A woman who was 54 years of age was known to have a small hiatal hernia with reflux and the symptoms of peptic esophagitis. Two days before her final hospital admission, she started vomiting and had severe hematemesis. The emergency roentgenologic examination of the patient, in recumbent position while blood was being transfused, showed a medium-sized hiatal hernia with massive reflux of gastric content into the esophagus (fig. 7). No other source of bleeding was found in the stomach and duodenum. At operation no bleeding lesion was found in the stomach. Severe hemorrhage recurred after operation, and neither the use of a compressing balloon tube nor blood transfusions could save the patient.

At autopsy the chief findings were three long lacerations, the largest being 3 cm. in length, straddling the esophagogastric mucosal junction (fig. 8). In addition, at a slightly higher level in the esophagus, a healed longitudinal ulcer, 2.5 cm. in length, was seen; this extended into the gastric mucosa as a still active, irregularly shaped longitudinal ulcer, 1.5 cm. in length, of moderately chronic, rather superficial character. Furthermore, several smaller ulcers in various stages of healing were found in the lowermost portion of the esophagus.

This instance corresponds in every respect to the Mallory-Weiss syndrome. The patient suffered severe and eventually fatal hemorrhages from lacerations in the cardiac region of the stomach. Her illness was preceded and accompanied by heavy vomiting. The rhagadiform mucosal tears were of different age. Some apparently occurred immediately before death; others showed partial or complete healing. One showed healing in its esophageal portion but persistence and transition to a chronic peptic ulcer of the gastric portion. This patient was not an alcoholic.

The occurrence and role of the hiatal hernia in this connection has not yet been recognized by pathologists. It is well known that small and medium-sized hiatal hernias, if not incarcerated, are usually not found by the routine methods of autopsy. In the case here reported, the prosector, specifically alerted before dissection, was not able to make a statement as to the presence or absence of the small hiatal hernia shown by two roentgenologic examinations. This patient, as well as several in the series of Decker and co-workers,[17] had a good history of cardiac incompetency and peptic esophagitis. It is a fair assumption that a hiatal hernia is a prerequisite of Mallory-Weiss lacerations.

The history of retching and vomiting preceding Mallory-Weiss lacerations requires a qualification. In a patient with a hiatal hernia and wide hiatal ring, massive reflux may occur passively when the subject lies down, causing little or no subjective sensation of retching and no vomiting. Nevertheless, the hernia may be unduly stretched and the mucosa injured. Contrarily, even without a preexistent hiatal hernia, violent vomiting may produce transient herniation, followed by the sequence of events described above. If such a hernia is reduced after cessation of vomiting, it could not be recognized roentgenologically, and only gastroscopic examination or opening of the stomach would reveal the bleeding lacerations.

Bleeding, Anemia, and Hiatal Hernia

Carman and Fineman[1] mentioned bleeding and anemia in 3 of the 20 cases of their first report on hiatal hernia. Ohnell in 1926 saw gross hemorrhage in three of his cases of hiatal hernia and emphasized the causal relationship between hiatal hernia and hemorrhage. The attempted explanations, however, have been vague and unsatisfactory. There are apparently three sources or modalities of bleeding: (1) peptic esophagitis with superficial ulceration, (2) Mallory-Weiss lacerations, and (3) the chronic marginal ulcer. Bleeding from peptic esophagitis may be occult or manifest; it is, however, unlikely to become severe or life-threatening. On the other hand, Mallory-Weiss lacerations or chronic peptic ulcer may cause severe and even fatal hemorrhages. All three conditions may lead to severe anemia of the iron deficiency type.

Only in the case of the chronic marginal ulcer can the source of hemorrhage be directly seen roentgenologically. Thus, I have been very reluctant in the past to attribute upper gastrointestinal hemorrhages to either of the other two conditions connected with hiatal hernia. Increasing experience has taught me to assume such a causal relationship more often if I fail to find any other source of bleeding by careful examination of the alimentary tract. However, this diagnosis by probability and exclusion is not the only approach. Schmidt, Barrett, Benedict, and others have shown that not only the chronic peptic ulcer but also peptic esophagitis with superficial ulcerations and deep bleeding lacerations may be seen by esophagoscopy in the lower portion of the esophagus and herniated stomach.

Severe esophagogastric hemorrhages have been successfully treated by subtotal gastric resection, without identification of the source of bleeding during the operation or in the resected specimen. In several reports of these operations, it is mentioned that the esophagus was mobilized and pulled down. It is possible that a small hiatal hernia had been unintentionally repaired, and it is probable that after subtotal gastric resection with a well-functioning gastrojejunostomy there is less gastric juice, reduced acidity, less reflux, and less regurgitation if retching or vomiting do occur. After resection of the lower portion of the esophagus and esophagogastrostomy, recurrent peptic ulcer and esophagitis are less frequent if a considerable portion of the stomach has been resected (Sweet and co-workers).

Iron deficiency anemia, often of long duration and of marked degree, has been cured by repair of a hiatal hernia (Harrington[5]; Dreyfuss[18]). It is believed that the reasoning on the sources of bleeding in the presence of hiatal hernia, as presented here, provides a sound rationale for these surgical treatments.

Esophageal or Marginal Ulcer

The so-called peptic ulcer of the esophagus has been explained classically by the occurrence of islands of gastric mucosa in the lower portion of the esoph-

agus. It was assumed that either the secretion of these mucosal islands with its autodigestive capacity or regurgitant gastric juice caused a peptic ulcer in the ectopic mucosa. One cannot deny this possibility for a few individual cases. These "marginal ulcers," however, usually occur on the gastric side of the junction of esophageal and gastric mucosa, as has been convincingly shown by Barrett.[4] At least three-fourths of the circumference of these ulcers is usually formed by gastric mucosa, and their location at the upper end of a hiatal hernia has been enigmatic so far. Why should a peptic ulcer occur just in the uppermost portion of the stomach where the incoming saliva constantly dilutes the gastric juice?

Mallory and Weiss[5] considered the possibility that some of the lacerations of the type observed by them might develop into chronic peptic ulcers. Various degrees of healing and chronicity have been observed. Numerous reports describe various stages, ranging from acute mucosal ulcerations of the cardia to chronic callous ulcers there; often these ulcers are described as being oblong. In the case reported here, one longitudinal ulcer was seen healed on the esophageal side, while in transition to a chronic peptic ulcer on the gastric side. Thus, it is plausible to assume that these marginal ulcers have originated from Mallory-Weiss lacerations, possibly even from repeated tears at the same place. The esophageal portion, if there were any, would heal, while the gastric portion would become a chronic peptic ulcer under the constant influence of peptic irritation. Allison and Johnstone illustrate in color the surgical specimen of such a marginal ulcer on the gastric side; I have observed two almost identical cases.

Summary and Conclusions

This discussion, coordinating old and new observations, is aimed at opening new avenues of thinking that may lead to more rational and successful treatment of the hiatal hernia complex. The precise manner of treatment is beyond the scope of this discussion. Treatment must obviously be oriented toward three aims: (1) reduction in quantity and peptic activity of the gastric juice, (2) prevention or reduction of gastric reflux by conservative measures, and (3) surgical repair of the hernia and hiatal ring.

A distinction must be made between the morphological (anatomic) cardiac opening and the functional or physiological cardia. Small and medium-sized hernias are common. In hiatal hernia, the dislocated "internal sphincter" of the cardia, deprived of its support by the diaphragmatic muscular ring, its "external sphincter," often becomes incompetent. Reflux of gastric juice and peptic esophagitis are responsible for "the symptoms of hiatal hernia" and the late sequelae of stricture and shortening of the esophagus. Copious reflux, with or without vomiting, may overdistend the herniated pouch and the slipped internal sphincter and produce mucosal lacerations of the Mallory-Weiss type. Bleeding (manifest or occult) leading to anemia may originate from these lacerations or from severe esophagitis. The marginal ulcer at the esophagogastric junction in hiatal hernia is probably a Mallory-Weiss laceration that has become chronic by peptic irritation.

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Hazards of Mineral Oil Aspiration.—In spite of the attention which has been directed toward this subject, the medical profession in general has been slow to develop an awareness of the disorder. In many, if not most, of the reported cases in adults, the presence of a lipoid granuloma was not considered or even suspected prior to surgery. . . . When lipid substances gain entrance to the lung the tissue response which is invoked may vary from (1) an acute pneumonitis to (2) a chronic diffuse pneumonitis to (3) a chronic localized granuloma, depending on the type of oil, the quantity, the frequency with which it enters the lung, and perhaps the age of the patient. . . . Localized lipoid granulomas apparently occur as the result of repeated aspiration of small quantities of a relatively inert material which has a large molecular size and thus cannot be readily transported from the lung or metabolized. These lesions are therefore relatively permanent and may be first detected in the course of a routine roentgenographic examination many years after the source of oil has been removed and its history almost forgotten. Such a lesion assumes particular importance in that it frequently cannot be distinguished from a pulmonary neoplasm. In fact, the manner in which lipoid granuloma may mimic bronchogenic carcinoma is truly amazing, and . . . the diagnosis is not only difficult but at times may be impossible without resort to surgical exploration and direct biopsy of the lesion.—H. A. Buechner, M.D., and L. H. Strug, M.D., Lipoid Granuloma of the Lung of Exogenous Origin, *Diseases of the Chest*, April, 1956.

CLINICAL NOTES

DIATRIZOATE SODIUM, A NEW UROGRAPHIC CONTRAST MEDIUM

Everett E. Seedorf, M.D.
and
Eldon O. Bradfield, M.D., Temple, Texas

The history of excretory urography has been reviewed by Braasch and Emmett.[1] Sodium iodomethamate (Neo-Iopax) and iodopyracet injection (Diodrast) were the excretory urographic mediums used for many years in the United States, but these were replaced by sodium acetrizoate injection (Urokon) because of its capacity to produce urograms of better quality. In August, 1954, we were invited to assist in the investigation of a new urographic contrast medium, diatrizoate sodium (Hypaque). This medium is a highly water-soluble white crystalline solid that contains iodine (59.87%). The preparation is dispensed in ampuls containing 30 cc. of a 50% solution. In our initial investigation, we gave intravenous injections using these ampuls to 200 patients. Experience demonstrated that an injection time of three to five minutes was desirable. For each patient, the temperature, pulse rate, respiration rate, and blood pressure were recorded before and 15 minutes after an injection. In no instance was there an appreciable variation that could be attributed to the effect of the drug. In a small number of patients, however, a few reactions were observed. These symptoms were of about the same frequency and mild nature that we previously had observed from the routine use of sodium acetrizoate, using 20 to 25 cc. of a 30% concentration.

In our investigation of diatrizoate sodium, we immediately and consistently observed marked improvement in the quality of excretory urograms. Films exposed 5, 10, and 15 minutes after injection of the medium were graded as poor, fair, good, or excellent. Urograms were rated poor when there was no visualization or there were only faint shadows and fair when visualization of segments of the urinary system was unsatisfactory for diagnostic purposes. If there were faint but distinct outlines of the urinary organs or if sufficient segments were visualized so that a positive diagnosis could be made, the quality was considered good. When there were exceptionally bold outlines of the ureters as well as of the pelvis and calices of the kidneys and the urograms were equal to or superior to retrograde pyelograms, they were rated excellent.

Of urograms produced with sodium acetrizoate, using the 30% solution, only 38% were considered good or excellent; whereas 94% of the urograms produced with diatrizoate sodium, using ampuls containing 30 cc. of the 50% solution, were of good or excellent quality. Bold shadows were produced on the films exposed five minutes after injection of diatrizoate sodium. This medium appears to be excreted from the kidneys and ureters more slowly than sodium acetrizoate and, therefore, outlines the urinary excretory system more consistently and completely even on the films exposed 10 and 15 minutes after injection. This seems to be an important factor contributing to the higher percentage of good and excellent diagnostic urograms produced with diatrizoate sodium.

It was presumed that the superior quality of urograms produced by diatrizoate sodium probably was due to the increased iodine content in the dosage. By calculation, it is shown that approximately 6 gm. of iodine is contained in a 20-cc. dose of a 50% solution of diatrizoate sodium or a 30-cc. dose of a 30% solution of sodium acetrizoate. Accordingly, a group of 50 patients was given the reduced dosage of diatrizoate sodium (20 cc. of a 50% solution) and a second group of 50 patients was given the increased dosage of sodium acetrizoate (30 cc. of the 30% solution). In the first group, 84% of the urograms were graded good or excellent; in the second group, 86% of the urograms were of good or excellent quality.

TABLE 1.—*Incidence of Good and Excellent Urograms with Urographic Mediums*

	Sodium Acetrizoate	Diatrizoate Sodium	Diatrizoate Sodium	Sodium Acetrizoate	Sodium Acetrizoate
No. of patients	100	200	50	50	50
Dosage, cc.	20-25	30	20	30	25
Concentration, %	30	50	50	30	50
Amount of iodine, gm.	5	9	6	6	8.25
Good and excellent urograms, %	38	94	84	86	74

Shortly after we completed this comparative study, sodium acetrizoate became available in 25-cc. ampuls of the 50% concentration. We investigated this dosage in a series of 50 patients. By calculation, this dosage contains more iodine than the previously studied ampuls of sodium acetrizoate, but, upon grading of the urograms, only 74% produced by the newer concentration were classified within the good and excellent group. Table 1 illustrates the percentage of good and excellent urograms produced by the varying dosages and concentrations of sodium acetrizoate and of diatrizoate sodium.

Reactions were recorded after the injection of sodium acetrizoate (20 to 25 cc. of the 30% solution) and diatrizoate sodium (30 cc. of the 50% solution). As additional variations in dosage and concentration of these mediums were studied, observation of the side-effects was continued (table 2).

Occasionally, momentary nausea was observed after all dosages and concentrations of both drugs, but, if injection of the medium was interrupted for a short interval, the nausea soon abated. Vomiting seldom occurred. Of far greater significance was the occurrence of vein-cramping observed in 22% of the patients given sodium acetrizoate (25 cc. of the 30% solution). This symptom occurred more often with the 50% solution than with the 30% solution of this drug, probably because there was a greater concentration of the medium

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Read before the Section on Radiology, Texas State Medical Association, Fort Worth, April 26, 1955.

within the fluid. Diatrizoate sodium was less prone to produce cramping of the veins. Itching sensations and urticaria were more common with sodium acetrizoate, but in most instances these symptoms disappeared within a few minutes after injection of the medium was completed. One patient experienced a short episode of sneezing after the administration of diatrizoate sodium.

TABLE 2.—*Incidence of Symptoms from Urographic Mediums*

	Sodium Acetrizoate	Diatrizoate Sodium	Diatrizoate Sodium	Sodium Acetrizoate	Sodium Acetrizoate
No. of patients	100	200	50	50	50
Dosage, cc.	25-30	30	20	30	25
Concentration, %	30	50	50	30	50
Side-effects, %					
Vein cramp	4	1	2	4	22
Nausea	4	6	8	4	18
Urticaria	2			4	10
Itching sensation	2	1	2	4	8
Flushing of skin		?	?	2	
Extreme pallor					2
Choking sensation				2	2
Sneezing		1			

Summary

From our study of urographic contrast mediums, we concluded that 30 cc. of a 50% solution of diatrizoate sodium (Hypaque) produces urograms of superior quality in a greater percentage of patients than can be obtained with 20 to 25 cc. of a 30% solution of sodium acetrizoate (Urokon) and slightly better urograms than were obtained with 25 cc. of a 50% solution of sodium acetrizoate. Probably because the medium is eliminated more slowly, the ureters are vizualized more clearly when diatrizoate sodium is used. There are few side-effects from diatrizoate sodium, particularly when the solution is not injected too rapidly. Objectionable reactions to sodium acetrizoate in doses of 25 cc. of the 50% concentration included a higher incidence of vein-cramping, nausea, and urticaria.

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The sodium acetrizoate used in this study was supplied as Urokon sodium, 50% solution, by Mallinckrodt Chemical Works, St. Louis, and the diatrizoate sodium was supplied as Hypaque by Winthrop-Stearns, Inc., New York.

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MOBILE RADIOTRANSLUCENT LITTER-TABLE WITH BUCKY DIAPHRAGM

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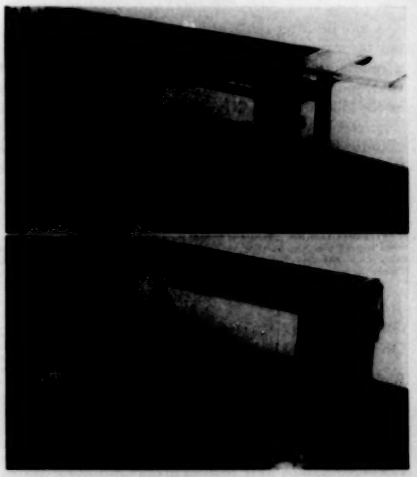
Ruth Hammerschlag, R.T.
and
Maxwell H. Poppel, M.D., New York

A mobile radiotranslucent litter-table with a Bucky diaphragm was constructed in our department as a result of a continually growing need for better radiographic procedures for bedside use and adaptable to the limitation of motion in seriously ill patients needing radiographic studies. Our table is also adapted for magnification techniques. We had investigated commercially available tables and had found nothing meeting our requirements. Several radiotranslucent tables obtainable on the market were of the type with supports under the table preventing use with an adjustable Bucky diaphragm stand. Our basic table is sufficiently strong to be safe for use with a mobile Bucky diaphragm stand, and it may be equipped with an attached Bucky diaphragm as we have done.

The table is constructed with a radiotranslucent top mounted on solid legs at the extreme ends and is equipped with lock wheels. For the comfort of some patients with back injuries, a radiotranslucent foam rubber pad covering the length of the table has been provided. At one end there is an extension for head radiography that allows for placement of a cassette for lateral skull projections without turning the patient. The metal trim around the table top permits mounting of magnetic cassette holders that aid in obtaining difficult views. Two vertical rods are located below the table top, one at each end; running between these is a horizontal unit with two rods supporting the Bucky diaphragm, which can be moved on these rods and travel the table length. This entire horizontal assembly can be raised and lowered on the vertical rods and can be locked in position directly below the table top for conventional work or at varied distances for magnification studies.



Litter-table, *A*, with Bucky diaphragm in conventional position and the head support extended and, *B*, with diaphragm in position for magnification studies and head support dropped.

From the Radiology Service, Veterans Administration Hospital, Bronx (Drs. Stein and Poppel and Miss Hammerschlag), and New York University College of Medicine (Drs. Stein and Poppel).

This table may be used at the bedside with any mobile radiographic machine. Any regular 110-volt wall outlet or adapter plug in a lighting fixture can be utilized. A hand switch from an old x-ray machine used on an extension cord enables us to operate the diaphragm away from the table and near the x-ray control. Poor radiographs resulting from body pressures against mattresses and pillows and inaccurate direction of rays due to uncontrollable angulation are eliminated by use of this solid-surface table. Cassettes are easily placed without disturbing the patient.

Seriously ill patients need not be moved from bed to litter, from litter to x-ray table, from table back to litter, and from litter back to bed. Patients are moved only from bed to new radiotranslucent litter table and back to bed. Those who are very seriously or critically ill can be satisfactorily radiographed without removal from the ward; others are brought to the x-ray department on the litter table. This mobile radiotranslucent litter table has been used in many unanticipated ways. It has been substituted for conventional equipment during temporary breakdown, has simplified the radiography of difficult cases, and often has been used in conjunction with any regular tilt table for special decubitus views of the recumbent abdomen such as are obtained in gallbladder studies with the Kirklin position during cholecystography.

Summary

A mobile litter-table utilizing the Bucky diaphragm has been constructed primarily for bedside use when a minimum of movement of the patient is desired. Conventional and magnification studies can be made, as the diaphragm can be locked in various positions. Cassettes can be easily placed in position. Magnetic cassette holders can be placed along the rim of the table. An extension of the table permits radiographic studies of the skull.

130 W. Kingsbridge Rd., Bronx 68 (Dr. Stein).

Mr. James Douglas, Technical Supervisor, assisted in this project; representatives of the Sommerville Veterans Administration Depot aided in the fabrication and installation of the Bucky diaphragm assembly; and the Picker X-Ray Corporation assisted in the construction of the basic table.

OBSTRUCTED ENDOTRACHEAL TUBE DEMONSTRATED BY ROENTGENOGRAM

Richard C. Thompson, M.D., San Mateo, Calif.

The vexing problem of a partially obstructed endotracheal tube has been encountered twice recently during the course of administration of anesthetics. Roentgenograms were helpful in demonstrating exactly why the tube was obstructed and what happened when the position of the tube was changed to correct the obstruction. In each case the bevel of the endotracheal tube rested against the anterior wall of the trachea. I have found only two references [1] to this problem.

Report of Cases

CASE 1.—A very ill 84-year-old male had a marked kyphosis and a rigid, extended cervical spine. Two large pillows were required to support his head. He was anesthetized and intubated in preparation for a laparotomy. The airway was clear until the metal elbow was disconnected from the curved plastic endotracheal tube to perform endotracheal suction. I assume that the unnatural position of the head caused this curved tube to rotate unnoticed. Soon after the angle piece was reconnected with the tube, the partial obstruction of the airway

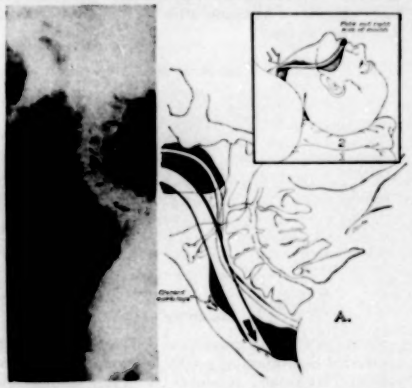


Fig. 1.—During administration of anesthesia in patient in case 1, the bevel of the endotracheal tube has inadvertently rotated anteriorly and has been obstructed by the anterior wall of the trachea.

was recognized; the reason was not apparent. The lungs could be inflated easily, but much of the exhaled gas escaped around the tube, necessitating an increase in flow from the machine. If respirations were not assisted, the patient became cyanosed. Roentgenograms were taken (fig. 1), and the tube was withdrawn and rotated until a clear airway was established (fig. 2).

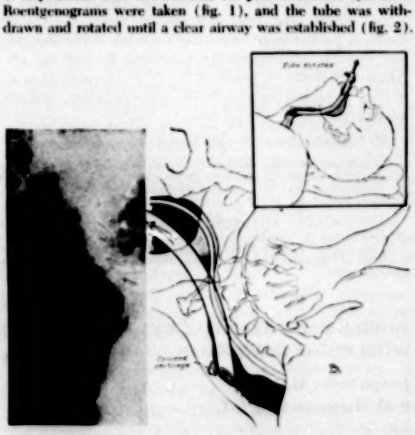


Fig. 2.—The endotracheal tube (case 1) has been withdrawn and rotated to establish a clear airway.

CASE 2.—A husky 42-year-old male was anesthetized for a disk exploration and spinal fusion. The plastic endotracheal airway was perfectly free until he was turned to the prone position. Partial obstruction of the endotracheal tube soon became apparent. The lungs could be readily inflated, but exhalation occurred, chiefly around the tube. Both inhalation

and exhalation were noisy, and exhalation was retarded and incomplete. Cyanosis became apparent, and a mixture enriched in oxygen was given until after x-rays were taken (fig. 3) and the position of the tube changed. In this case, to effect the proper change in position of the tube, the head was rotated to the opposite side and the tube was withdrawn approximately 2 cm. (fig. 4).

Comment

Insert *A* in figure 1 shows the exaggerated posterior curve in the trachea of the elderly edentulous man with extreme kyphosis; it is not surprising that the tube rotated to the position shown. This is clearly an unusual situation. Case 2 presented a situation that might occur more commonly than is generally recognized. In either the dorsal or prone position, when the head is turned sharply to the side as in certain orthopedic, intracranial, or otological operations, the hazard of obstruction due to apposition of the bevel of the tube to the anterior tracheal wall may occur. Moreover, if the neck is markedly extended, the trachea will curve posteriorly and a slight rotation of the tube may result in obstruction at the bevel. However, the routine use of fenestrated tubes[2] will make endotracheal anesthesia a safer procedure.

Summary and Conclusions

In the administration of anesthetics, the bevel of the endotracheal tube may lie against the anterior tracheal mucosa and cause obstruction when the patient's head is turned to the side or unusual circumstances cause rotation of the tube. A fenestrated tube should be selected that will ensure that the bevel faces posteriorly when the head is sharply rotated and extended in an unusual position. The outer end of the endotracheal tube should be marked or notched on the side of the bevel so that the relative position of the bevel will be apparent at all times. When the flow of gases through the tube is impeded, the possibility of apposition of the bevel against the tracheal mucosa should be considered and

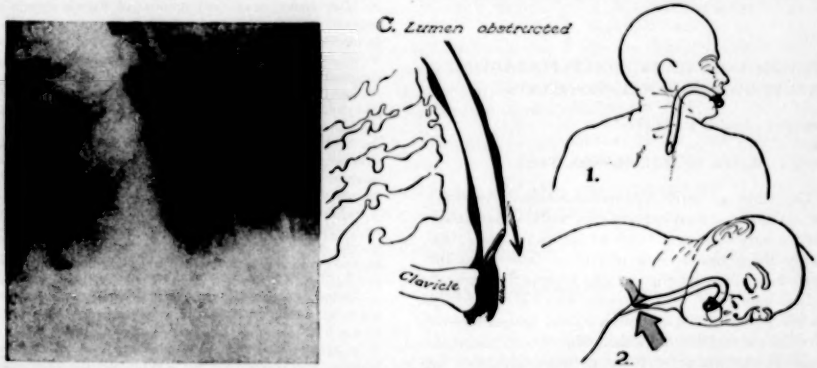


Fig. 3.—The patient in case 2 has been placed in the prone position with his head turned to the side. The rotation of the head was followed by obstruction of the endotracheal tube as the bevel came to rest against the anterior tracheal wall.

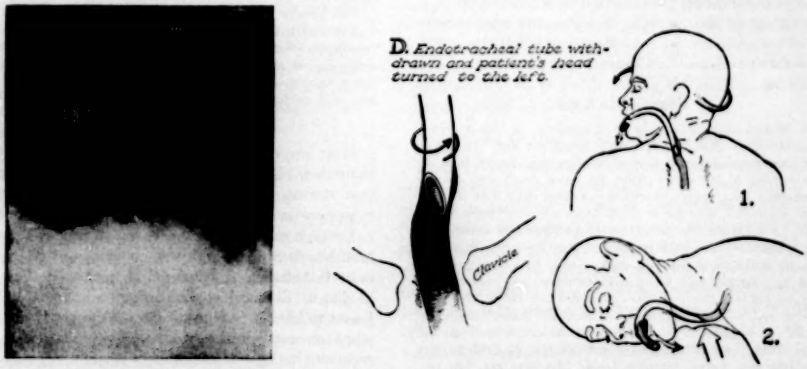


Fig. 4.—A clear airway has been established (case 2) by turning the head to the opposite side. The bevel then faced posteriorly.

some suitable manipulation employed to alter such a situation. Roentgenograms were helpful in these cases in demonstrating the cause of endotracheal obstruction.

545 Fairfax Ave.

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SIGNIFICANCE OF JAUNDICE FOLLOWING PANCREATODUODENAL RESECTION

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and
Elvin L. Shelton Jr., M.D., Houston, Texas

The value of radical pancreatoduodenal resection for malignant lesions causing obstructive jaundice has been a subject of some debate for many years. Recently there has been a revival of interest in this procedure following encouraging reports that indicate its use may result in a five-year survival rate of 38% for carcinoma of the ampulla of Vater and a five-year survival rate of 15% for carcinoma of the pancreas.[1] Even in the hands of those enthusiastic about the procedure, the recurrence of intra-abdominal symptoms following operation, particularly jaundice, has been taken as evidence of recurrence of disease. Whereas this will be the usual cause, such patients may develop jaundice on any etiological basis. The present case report is that of a patient who developed jaundice due to benign stricture of the common duct one year following pancreatoduodenal resection of a carcinoma of the ampulla of Vater and who is now alive and well five years following his initial surgery and three and one-half years following repair of the stricture.

Report of a Case

A 55-year-old white male was admitted to the Veterans Administration Hospital, Houston, Texas, on Oct. 11, 1950. His history revealed that he had been in good health until six weeks prior to admission, when he noted fever and general weakness. Temperature elevations occurred daily and at times were associated with frank chills. Approximately three weeks prior to admission the patient noted pruritus and jaundice of the scleras; subsequently he noticed that his urine was dark and his stools were light in color. There had been a 12-lb. (5.4 kg.) weight loss. Physical examination was noncontributory, except that the liver was palpated 4 cm. below the costal border and was slightly tender. Laboratory examinations revealed: hemoglobin level, 9 gm. per 100 cc.; serum amylase level, 26 units per 100 cc.; fecal urobilinogen, 21 Ehrlich units per 100 gm.; serum bilirubin level, 12.8 mg. per 100 cc.; alkaline phosphatase level, 19.3 Bodansky units per 100 cc.; thymol turbidity, 2 units; and cephalin flocculation test, negative.

From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the Veterans Administration Hospital (Dr. Jordan).

The anemia was corrected by blood transfusions. While the patient was being observed in the hospital, the serum bilirubin level decreased to 5.6 mg. per 100 cc. and then increased to 11 mg. per 100 cc. A clinical diagnosis of obstructive jaundice secondary to carcinoma of the duodenum or ampulla of Vater was made, and on Nov. 3, 1950, the abdomen was explored. The gallbladder was distended, as was the common bile duct. The pancreas appeared to be normal, but there was a 3-cm. crater-like lesion at the ampulla of Vater. No metastatic lesions were found. The head, neck, and portion of the body of the pancreas, 30% of the stomach, 2 cm. of common bile duct, and the first, second, and third portions of the duodenum were removed en bloc. The duodenal stump was closed, and a loop of jejunum was brought anterior to the colon for construction of an end-to-side choledochojejunostomy, an end-to-side pancreatojejunostomy, and an end-to-side gastrojejunostomy, with the latter anastomosis being approximately 35 cm. distal to the pancreatojejunostomy. The pathological diagnosis was columnar cell carcinoma of the ampulla of Vater. A biopsy specimen of the liver taken at the time of surgery revealed acute hepatitis with focal abscesses. Postoperatively the patient did well. All laboratory findings returned to normal levels, and within three months the patient gained 20 lb. (10.8 kg.).

In July, 1951, the patient returned to the hospital, complaining of chills, fever, and pruritus, having noted their onset two months before admission. At the time of admission he was asymptomatic and a thorough examination revealed no objective findings. He returned again in January, 1952, with similar complaints. A thorough reevaluation again revealed no abnormality. Scabies was thought to be the cause of the pruritus. However, when he was admitted for the third time on April 22, 1952, physical examination revealed icteric scleras. The serum bilirubin level was 2.7 mg. per 100 cc., and the serum alkaline phosphatase level was 32 Bodansky units per 100 cc. Other laboratory examinations were within normal limits. Surgical exploration was performed on May 9, 1952. Marked scarring at the site of the choledochojejunostomy, with a definite stricture of the common bile duct, was found. The area of stenosis was resected, and a reanastomosis of the common bile duct to the jejunum was performed. He was discharged from the hospital 15 days postoperatively after an uneventful convalescence.

This patient has been seen periodically since the last procedure and has remained in good health. There has been no recurrence of the jaundice or pruritus. He eats without difficulty, he has maintained his weight, and physical examination has remained within normal limits. He was known to be alive and well on Jan. 29, 1956, five years after his initial surgery.

Comment

Most surgeons treating intra-abdominal carcinoma limit their efforts at curative surgery to wide extirpation during the original procedure. Thereafter, if symptoms or signs suggesting recurrent intra-abdominal malignant lesions appear, the situation is considered hopeless. Although this conclusion is justified in most instances, an occasional patient who dies with a clinical diagnosis of recurrent carcinoma will be found to have a benign disease as the cause of death when an autopsy is performed, without evidence of recurrent malignant lesions. Consequently, a thorough evaluation of each patient should be made when new symptoms arise or old symptoms return.

The recurrence of jaundice following pancreaticoduodenal resection for carcinoma of the pancreas or carcinoma of the ampulla of Vater often denotes recurrence of the disease, but the patient we are re-

porting presents an example of a benign complication that may produce symptoms and signs suggesting recurrent malignant lesions. The development of a benign stricture is only one of the causes for the occurrence of jaundice after an operation. In the early postoperative period jaundice may be secondary to transfusion reaction, to improper construction of a choledochojejunostomy, or, more rarely, to transient postoperative edema of the stoma. Homologous serum jaundice and infectious hepatitis have produced the same alarming symptoms several weeks or even several months postoperatively. Ascending cholangitis may also occur. This will usually be accompanied by chills and fever. One rarely encounters obstruction of the external biliary tree resulting from a common duct stone. In recent years chlorpromazine (Thorazine)-induced hepatitis has complicated the problem, for the changes in liver function tests that occur are those commonly thought to be typical of an obstructive jaundice.

Furthermore, one occasionally encounters two independent primary carcinomas in the abdomen. One such case was reported by Brunschwig,[2] wherein a radical resection for carcinoma of the ampulla of Vater with lymph node metastases was performed in 1943. Two years later a palpable abdominal mass developed that, upon clinical examination, was thought to be a metastasis from the original lesion. However, a laparotomy was performed, and a second primary carcinoma was found in the ascending colon with nodal metastasis. A right hemicolectomy and node dissection was performed. The patient was alive and well eight years following the original pancreatoduodenectomy and six years following the hemicolectomy.

In many instances, exploratory laparotomy may be the only means of positively establishing a diagnosis, and our experience leads us to advocate reoperation, unless there are proved distant metastases or unless other definite contraindications to operative intervention exist. Cases such as these reported are uncommon, and no one physician is likely to see many. However, such patients will be saved only if a positive diagnosis is established and proper treatment is instituted.

Summary

A patient with obstructive jaundice resulting from carcinoma of the ampulla and treated by pancreatoduodenal resection developed recurrent obstructive jaundice approximately one year following surgery. He was found to have a benign stricture of the common duct, which was successfully treated, and he is alive and well five years following his initial surgery. This case demonstrates the necessity of careful evaluation and treatment of patients with symptoms suggesting recurrent malignant lesions.

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following paper was presented at the symposium, "Some Inorganic Elements in Human Nutrition," in Nashville, Tenn., April 4, 1955. This symposium was sponsored jointly by the Nashville Academy of Medicine, the Vanderbilt University School of Medicine, and the Council on Foods and Nutrition. This report is the third of the series, others of which appeared in THE JOURNAL *April 21 and June 9, 1956.*

EUGENE H. STEVENSON, M.S.
Acting Secretary.

METABOLISM AND REQUIREMENTS OF IRON IN THE HUMAN

Carl V. Moore, M.D.
and
Reubenia Dubach, Ph.D., St. Louis

Disturbances of iron metabolism may lead to the development of either iron deficiency or iron excess in the body. The latter state, although comparatively rare, is of increasing clinical importance. It occurs in hemochromatosis, in transfusion hemosiderosis as a result of prolonged excessive iron therapy, and as a part of cytosiderosis, an interesting nutritional abnormality found among the Bantus in Africa. Iron deficiency anemia is one of the most common nutritional deficiencies and one of the most prevalent anemias the world over. In order to understand the pathogenesis and treatment of these disorders, one must know the dietary requirements for iron, how the body uses iron, and how the body normally maintains a positive balance while providing safeguards against excessive accumulations of the metal.

An Outline of Iron Metabolism

Iron, as an essential component of hemoglobin, myohemoglobin, the cytochromes, and other enzyme systems, is required for the important physiological functions of transport of oxygen and cellular respiration. The body of a normal, adult human contains approximately 3 to 5 gm. of iron. Roughly 55% of this total is present in the circulating hemoglobin, about 10 to 20% in myohemoglobin, and a small amount in cells in the form of respiratory enzymes. The remainder is stored chiefly in the liver, spleen, kidney, and bone marrow.

The human absorbs iron mostly, if not entirely, in its ferrous form.[1] Reduction of food iron from the

From the Department of Medicine, Washington University School of Medicine.

ferric to the ferrous state begins in the stomach and continues in the intestine. The actual amount of iron absorbed from the stomach is unknown; absorption is probably greatest in the upper portion of the small intestine and progressively smaller in the more distal segments of the gastrointestinal tract. The reason for this diminishing gradient has never been adequately defined. It may be that the ileum, for instance, is not so efficient as the duodenum in absorbing iron, but the difference may be due solely to the fact that insoluble, complex iron salts are formed by the time the iron reaches the ileum.

Patients with iron deficiency or hypochromic anemia absorb inorganic iron more efficiently than do normal persons.[2] The intestinal mucosa serves to some extent as a regulator of iron balance, but the mechanism by which the intestinal mucosa absorbs iron is incompletely understood. The most likely theory is that iron enters the mucosal cells by combining with a protein, apoferritin, to form ferritin, a compound in which colloidal iron hydroxide–iron phosphate micelles are

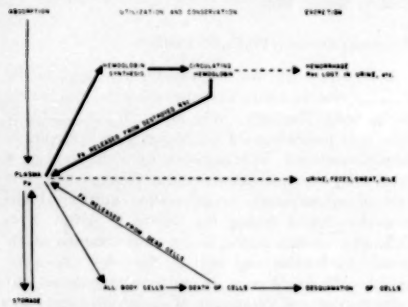

Fig. 1.—Schematic outline of iron metabolism.

bound to the protein in amounts up to 23% by weight.[3] It is suggested that apoferritin is constantly being formed and broken down; according to this hypothesis, its degradation stops when it combines with iron to form ferritin. The presence of ferritin is thought to cause a block of further absorption of iron until the ferritin can give up its iron to the blood stream, a process that presumably occurs with greater rapidity when iron deficiency exists. This regulatory mechanism seems selective enough to be more efficient when the body requires larger amounts of the metal. That it is only a partial control, however, is indicated by numerous instances in which absorption is relatively great even though the stores of iron are adequate or even large. One must be careful to guard against the erroneous idea that normal persons absorb no iron at all.

Iron is absorbed directly into the blood stream rather than through the lymphatic channels (fig. 1). When it passes into the blood plasma, it is oxidized to the ferric state and combined with a specific iron-binding protein, a beta-1 globulin that has been called transferrin, siderophilin, or simply "the iron-binding protein." Each molecule of this specific plasma protein can combine with two atoms of iron; there is enough of it in 100 cc. of plasma to bind from 300 to about 420 mcg. of iron. The amount of iron in plasma,

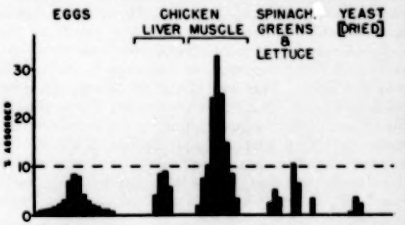

Fig. 2.—Absorption of radioactive iron (Fe^{59}) from food by normal persons. (Reproduced by permission of the *American Journal of Clinical Nutrition.*)

however, normally varies from 50 to 180 mcg. per 100 cc.; only a portion of the beta-1 globulin, therefore, is bound.

The iron in plasma is transport iron, the hub of iron metabolism. From the plasma, iron can go to organs of storage; it can be utilized, or it can be excreted. A relatively large percentage of the iron goes to the bone marrow where it is used for hemoglobin synthesis, but some is taken up by other cells of the body for the formation of cellular enzymes. The amount of iron in plasma is small, but the turnover rate is rapid, averaging about 0.56 mg. per kilogram of body weight per day.[4] This quantity in a man who weighs 70 kg. (154 lb.) would be 39 mg. per day. Since a normal man

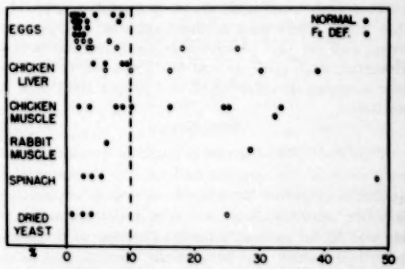

Fig. 3.—Absorption of radioactive iron (Fe^{59}) from foods by normal persons and persons deficient in iron.

uses from 20 to 25 mg. of iron per day to make hemoglobin, it is evident that the plasma iron can easily supply the bone marrow's need.

One very important characteristic of iron metabolism is the high degree to which the body conserves the metal. When red blood cells are destroyed, almost all the iron released from hemoglobin is reutilized.

Iron released from other cells that die is similarly conserved. Small but significant amounts are excreted from the body. Whenever red blood cells are lost, as in urine or by hemorrhage, or whenever cells are desquamated from the surface of the body or from the gastrointestinal tract, the iron that they contain must be considered to have been excreted.

It has been demonstrated that (1) the amount of iron stored in the tissues of a healthy adult is approximately 1 gm.; (2) the liver and spleen constitute the chief storage sites; (3) storage iron is found intracellularly in a protein complex as ferritin and as hemosiderin.[5] The chemical identity of hemosiderin has not been established, but the suggestion has been made that it may be merely a condensation or clustering of ferritin molecules. In the liver and spleen of normal animals, there is a slight preponderance of ferritin over hemosiderin iron.[5] With larger concentrations of iron in the tissues, this ratio is reversed, and at high levels the additional storage iron is deposited as hemosiderin. Of great physiological importance is the fact that both compounds are capable of being mobilized by the body for hemoglobin synthesis when the need for iron exists.

This brief, schematic summary of some of the major characteristics of iron metabolism has emphasized how tenaciously the body conserves iron. It is evident that, if only small amounts of the metal are lost or excreted, the amount absorbed is of prime importance in the prevention of either iron deficiency or overload.

Absorption from Foods

Although a great deal has been learned about the absorption of iron from inorganic salts, we must know how well the metal is absorbed from foods before we can understand the problems of iron nutrition. This information has been very difficult to obtain. Some workers have measured the portion of food iron that can be ionized by dilute hydrochloric acid on the assumption that only ionizable iron can be assimilated. This method is indirect; it ignores the possibility that enzymatic digestion in the intestine may free an additional portion of the food iron, and it cannot indicate what percentage of the ionized iron will be absorbed. Balance studies have been helpful. McMillan and Johnston [6] found that about 12% of the iron in spinach or in a basal diet was absorbed by young college women. Iron is so ubiquitous, however, that the technical difficulties in such balance experiments are enormous.

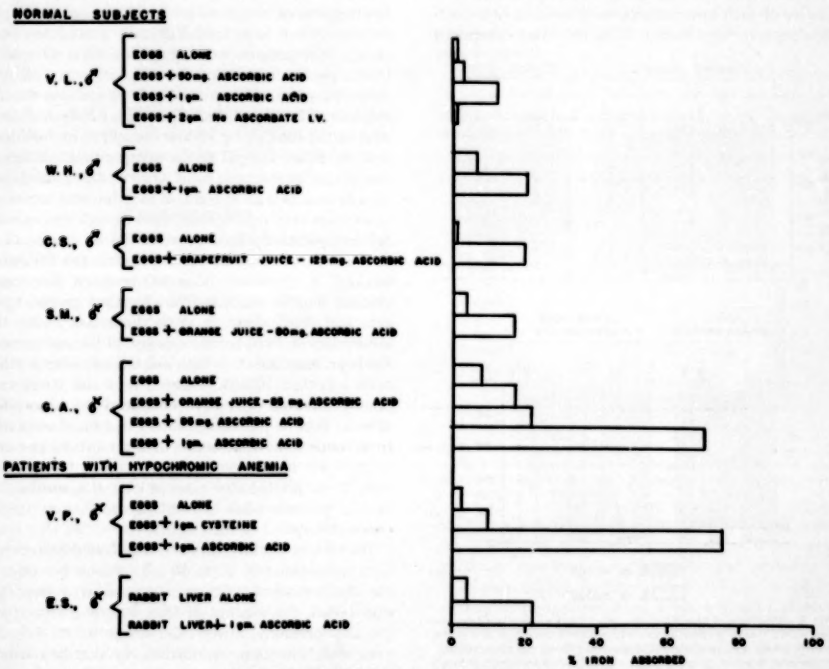

Fig. 4.—Effect of reducing substances on absorption of food iron.

Recently, more progress has been made with the use of radioactive iron (Fe^{59}). Foods containing Fe^{59} are obtained by growing vegetables in nutrient solutions to which the isotope is added or by injecting iron into hens so that eggs, liver, and muscle contain Fe^{59}.[7] These foods are cooked or prepared as they would be in a normal diet and are fed to fasting subjects. The unabsorbed radioactivity recovered in the feces and the maximum amount that appears in the circulating blood as newly synthesized hemoglobin are both measured. Figure 2 presents the results of a number of such observations, each column representing a separate experiment. With only two exceptions

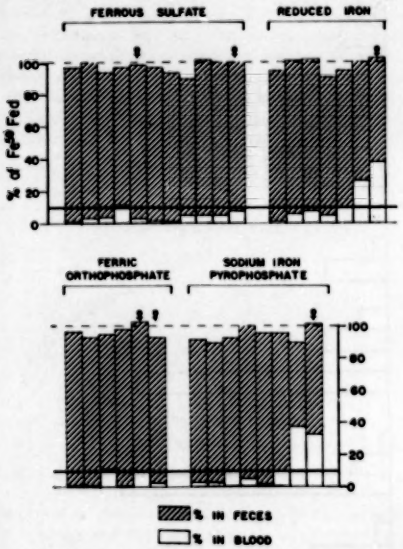

Fig. 5.—Absorption of four radioactive iron (Fe^{59}) preparations from enriched bread. Two of the four persons who absorbed more than 10% of the iron were young women whose loss of menstrual blood was above normal; the remaining two were two young men who had served repeatedly as blood donors. (Reproduced by permission of the *A. M. A. Archives of Internal Medicine.*)

—the most striking exception being from chicken muscle—less than 10% of the food iron was absorbed by normal persons. Similar observations of patients deficient in iron revealed that very few of them absorbed iron from eggs any more efficiently than did normal persons. In a few observations made with chicken liver, spinach, and dried (brewer's) yeast, it appears that patients with iron deficiency anemia tend to absorb these forms of food iron somewhat more efficiently (fig. 3). When other foods were fed at the same time as eggs, only citrus fruit juices, containing a relatively high concentration of ascorbic acid, augmented the assimilation of the Fe^{59} (fig. 4). The increased absorption produced by 200 cc. of orange juice and the increase produced by an equivalent amount of crystalline ascorbic acid were similar (see G. A., fig. 4). The addition of 0.25 to 1 gm. of crystalline ascorbic acid to a number of different foods increased iron absorption in every case, with perhaps a slightly greater effect in the subjects deficient in iron. It is suggested that ascorbic acid produces this result by more efficiently reducing ferric iron in food to the ferrous state.

A preliminary attempt has been made to evaluate the importance of gastric hydrochloric acid in the absorption of iron from food. For many years it has been taught that patients with hypochlorhydria or achlorhydria probably assimilate iron poorly. In such patients, however, we were not able to increase the absorption of iron by adding 60 cc. of 0.1 *N* hydrochloric acid to the food or by adding enough *N* hydrochloric acid to reduce the pH of the mixture to 1.5 before it was given by stomach tube. On the other hand, administration of 0.25 to 1 gm. of ascorbic acid increased absorption very significantly, even though this amount had comparatively little effect on gastric acidity.

These results can be summarized in the following manner. 1. Fe^{59} has been incorporated into eggs, chicken muscle, chicken liver, mustard greens, spinach, and dried yeast. 2. With three exceptions, the absorption of Fe^{59} from foods by 40 normal persons has been less than 20%; with only six exceptions it has been less than 10%. 3. Ascorbic acid and foods containing ascorbic acid have enhanced the absorption of food iron. 4. Persons deficient in iron absorb iron from foods somewhat better than do normal persons, particularly if the food iron is reduced by ascorbic acid. 5. In preliminary observations, the addition of acid in patients with hypochlorhydria has not influenced absorption of food iron.

The diet of healthy adults in the United States contains approximately 12 to 15 mg. of iron per day. If the aforementioned figures are used as a basis for calculation, the amount of iron absorbed from food per day probably varies from about 0.6 to 1.5 mg. Poor diet, infection, steatorrhea, or diarrhea would decrease this amount even further. The effect of steatorrhea in reducing the absorption of iron by patients with hypochromic anemia has been demonstrated recently.[8]

Of related interest are observations recently completed on the absorption of iron from bread baked with flour that had been enriched with Fe^{59}.[9] In the food fortification program in the United States, iron is added as powdered metallic iron, as sodium ferric pyrophosphate, as ferric orthophosphate, or as ferrous sulfate in amounts sufficient to provide 6 to 8 mg. of iron per pound loaf of bread; however, the effectiveness of this particular type of fortification has not been evaluated adequately, and several of the preparations are so insoluble that one wonders how valuable they

are. Each of the four iron preparations was obtained in radioactive form and baked into bread by a pilot bakery, along with other substances used in fortification. The baking process simulated as closely as possible that used by large commercial bakeries. Four slices of the bread were then fed to 32 healthy medical students and 3 persons with iron deficiency anemia, and absorption was measured. Twenty-eight of the 32 students absorbed and utilized between 1 and 12% of the iron, regardless of the form of iron added. The other four students assimilated 26 to 38% of the Fe^{59}, but there was reason to suspect that their iron stores were suboptimal (fig. 5). Apparently the various iron preparations are changed in the baking process, probably to a complex salt, so that all are about equally effective. The three patients with iron deficiency anemia assimilated 45 to 64% of the iron taken. Addition of 1 gm. of ascorbic acid to the bread eaten by six of the healthy persons increased the absorption of iron two to three times.

Excretion of Iron

Because iron is conserved so tenaciously and because the amount excreted is small, many people have mistakenly assumed that no iron whatever is lost from the body except as shed blood. The error of this assumption becomes obvious from the following considerations. All cells in the body contain iron. When leukocytes and epithelial cells are discharged in body secretions, when erythrocytes appear in urine, when cells are desquamated from the skin or the mucosa of the intestinal tract, and even when hair grows, some iron is lost. Attempts to estimate this amount, and to determine in addition how much is excreted in other ways have proved to be very difficult. The metal is so ubiquitous that it has been almost impossible to differentiate between excreted iron and that present because of contamination or failure to be absorbed. Fe^{59} has provided a partial solution to the problem.

The isotope has been injected in tracer amounts into the veins of normal subjects and patients with hypochromic or hemolytic anemias.[10] Five-day fecal collections were made at intervals for up to 150 days; this long period was used because most of the injected Fe^{59} was promptly synthesized into hemoglobin, and it was essential to continue the observations longer than the 120-day lifespan of erythrocytes. Every fecal specimen of every person contained a detectable amount of radioactivity; the amount averaged 0.01% of the dose per day for normal persons. Three patients who were deficient in iron excreted much less, whereas one young woman with a hemolytic (sickle cell) anemia excreted more. No significant increase in fecal radioactivity was detected at or near the 120th day after the injection. However, it is difficult to calculate from these figures the fecal excretion of all body iron—inert as well as radioactive. Two calculations were made: one from the ratio of total hemoglobin iron to radioactive hemoglobin iron, the other from the ratio of estimated total body iron to the injected dose of the isotope (fig. 6). Fecal excretion calculated in these ways for normal persons varied from 0.3 to 0.5 mg. per day. For patients deficient in iron, the value was about one-tenth as much. Although these calculated values are estimations, it is reasonably certain that they do not vary from true figures by more than 100%. With this method of determination, one cannot differentiate between the following three possible sources of fecal iron: (1) true excretion, (2) desquamated mucosal cells, and (3) iron delivered to the duodenum via the bile and not completely absorbed.

Some of the injected Fe^{59} was also found regularly in sweat for at least 320 days, the longest time after administration that a collection was made. The amount was small but definitely measurable. We were not able to determine whether it came from sweat glands by a process of true excretion or from desquamated epithelial cells. Calculations indicated that under normal conditions the total iron lost from dermal surfaces is certainly less than 1 mg. per day and probably not more than 0.5 mg. Radioactivity could also be detected in hair clippings obtained several months after the injection of radioiron and washed with dilute hydrochloric acid to free them from surface (sweat) contamination. The small amount of iron found in urine must also be considered.

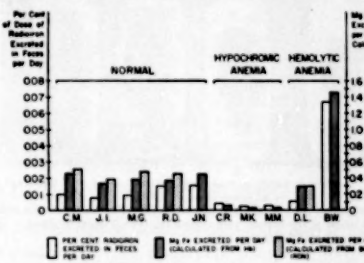

Fig. 6.—Average daily radioiron excretion and calculated total iron excretion of 10 human subjects. (Reproduced by permission of the *Journal of Laboratory and Clinical Medicine*.)

One can estimate that the adult male loses or excretes a total of 0.5 to 1.5 mg. of iron per day; the median value of 1 mg. is probably not in error by more than 20 to 25%. Menstrual blood flow of 35 to 70 cc. every 28 days in a normal woman with a hemoglobin value of 12 gm. would account for an additional average loss of 0.5 to 1 mg. per day. The donation of blood for transfusion purposes has become so common that this type of blood loss must also be considered in any discussion of excretion of iron. When 500 cc. of blood with a hemoglobin value of 15 gm. per 100 cc. is withdrawn, the donor loses approximately 0.25 gm. of iron. This amount spread evenly

over a year averages about 0.68 mg. per day. It is evident that multiple donations, not covered by supplemental iron, would constitute a severe drain on the body's iron economy.

Observations on humans emphasize the fact that nutritionally significant amounts of iron are lost or excreted, but these studies are admittedly semiquantitative. The only truly quantitative experiments have been done by Finch and his associates on mice.[11] They have obtained surprising results by using a counter that permitted them to make measurements of radioactivity on the whole animal. Mice were killed at intervals for 300 days after injection of Fe^{59}; only half of the radioactivity could be recovered from the whole carcass after about 140 days.[11a] Furthermore, under experimental conditions of induced iron overload, the amount of iron excreted was increased proportionally to the increase in body iron.[11b] These data suggest that, in the mouse, excretion, as well as absorption, plays an important role in maintaining normal iron balance. All available evidence indicates that the human excretes iron more sparingly, even though in nutritionally significant amounts.

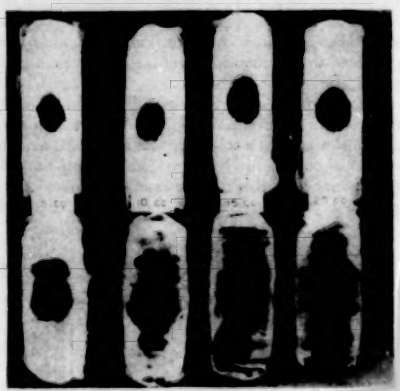

Fig. 7.—Pads prepared to show that abnormal amount of blood lost in menstrual flow may be accepted as normal. Blood in the amounts of 5, 10, 15, and 20 cc. was placed on pads. The four pads at the top were not disturbed; those at the bottom were rubbed together at edges to simulate agitation occurring with walking.

Importance of Nutrition in the Pathogenesis of Iron Deficiency Anemias

Although the data presented for the absorption of iron from food and for the excretion of iron are incomplete and provide approximations only, they permit a better evaluation of the importance of nutritional factors in the pathogenesis of iron deficiency than has been possible previously. If the adult male absorbs an average of 10% of the iron in a diet that contains 12 to 15 mg. per day, he retains 1.2 to 1.5 mg. Since he excretes only about 1 mg. or less of iron per day, he maintains a positive balance rather easily. The adult female, however, during the years of menstruation and child bearing, tends to eat less and loses additional amounts. During gestation a mother furnishes her fetus with about 0.3 to 0.5 gm. of iron, or between 1 and 2 mg. per day. The normal volume of menstrual blood is approximately 35 to 70 cc. If the hemoglobin value of that blood is 12 gm. per 100 cc., then 14 to 28 mg. of iron is involved. Spread evenly over a 28-day menstrual cycle, this amount equals 0.5 to 1 mg. per day. Iron balance in a young woman, therefore, is precarious; poor diet or poor absorption may lead to iron deficiency even though menstrual loss remains normal. Frequent pregnancies or any increases in menstrual flow make her more susceptible. Furthermore, women are often unaware of the fact that they might be losing several times the normal amount of menstrual blood. Menstrual pads absorb blood so efficiently that false impressions are obtained. The pads in figure 7 were prepared by adding onto their surfaces 5, 10, 15, and 20 cc. of blood, respectively. The four at the top were not disturbed. Those at the bottom were rubbed together at the edges to simulate the agitation that might occur with walking. In no instance did the blood soak through more than three-fourths of the material. Women physicians who inspected and watched the preparation all agreed that at least the pads to which 10 cc. had been added would be considered "normal." It is evident that a woman who uses 10 to 15 pads per period might easily lose more than 100 cc. of blood without being aware of any abnormality. The authors have seen two intelligent, medically trained women with hypochromic anemia whose extracted pads contained in excess of 200 cc. of blood per period; neither one had been aware that her blood loss was unusual.

Table 1.—*Calculated Time for Development of Dietary Iron Deficiency*

	Adult Man*		Postmenopausal Woman†	
Normal				
Total hemoglobin iron, gm.	2.5		1.9	
Storage iron, gm.	1		0.5	
Total, gm.		3.5		2.4
Iron deficiency‡				
Total hemoglobin iron, gm.	1.25		0.95	
Storage iron, gm.	0		0	
Total, gm		1.25		0.95
Deficit in hemoglobin and storage iron, gm.		2.25		1.45
Time required to produce deficiency, days§		2,250 (6.3 yr.)		1,450 (4 yr.)

* Hemoglobin, 15 gm./100 cc. Blood volume, 5,000 cc.
† Hemoglobin, 14 gm./100 cc. Blood volume, 4,000 cc.
‡ Hemoglobin, 7.5 gm./100 cc.
§ Assuming that no iron is absorbed and 1 mg. is excreted daily.

Since the body of an infant contains about

0.5 gm. of iron and that of an adult 3 to 5 gm., there must be a net gain during the first 20 years of life of 2.5 to 4.5 gm.; this net gain averages 0.12 to 0.22 gm. per year or about 0.35 to 0.6 mg. per day. In all probability, the positive iron balance maintained by normal children during their most active growth must be slight, and poor diet or poor absorption could readily produce iron deficiency.

It is much more difficult for iron deficiency to develop in the adult male or the postmenopausal female on a purely nutritional basis without any associated blood loss. The calculations in table 1, based on two hypothetical patients, an adult male and a postmenopausal woman, demonstrate that, if these two persons each excreted 1 mg. of iron per day and absorbed none at all, periods of six and four years, respectively, would pass before they became deficient enough to have only 7.5 gm. of hemoglobin per 100 cc. These figures ignore the evidence that as patients become deficient in iron they excrete smaller amounts of the metal. Any iron contained in the deficient diet, furthermore, would tend to be assimilated with greater than normal efficiency unless there were a serious absorptive defect in the intestinal tract. Both factors would considerably delay the appearance of iron deficiency anemia. One must admit, however, the theoretical possibility that men or postmenopausal women who consume very deficient diets or who have absorptive defects could, over a period of many years, develop iron deficiency on a nutritional basis alone. On the other hand, it seems far more likely that patients with inadequate diets or poor absorption also lose small amounts of blood that go undetected. The bleeding may be slight and intermittent, so that diligent search is required for its detection. There is some evidence that blood added in small amounts to the stomach may be so completely digested that tests for occult blood in the feces remain negative.[13] With hemorrhage, even though slight, inadequate iron intake or absorption becomes of major importance in the pathogenesis of hypochromic anemia.

TABLE 2.—*Recommended Dietary Allowance of Iron**

	Iron, Mg.
Man, 70 kg. (154 lb.)	12
Woman, 56 kg. (123 lb.)	12
Pregnancy (latter half)	15
Lactation	15
Child, yr.	
Under 1	6
1-3	7
4-6	8
7-9	10
10-12	12
Over 12	15

* Recommended Dietary Allowances, A Report of the Food and Nutrition Board, Publication 302, National Research Council, 1953.

It is evident from the considerations reviewed in this section, from the incomplete state of our knowledge about the absorption of iron from foods, and from the meagerness of our information about excretion of iron in the human that a precise definition of dietary iron requirements is not yet possible. The recommendations of the Food and Nutrition Board seem to be adequate, and they probably represent as good approximations as can be made at present (table 2). These quantities of food iron, however, do not provide a wide margin of safety except, perhaps, for the adult man and the postmenopausal woman.

Iron Overload

Iron overload is of increasing clinical importance.[13] It is discussed briefly herein because increased absorption of iron, sometimes associated with high oral intake of the metal, is of pathogenic importance in some forms of overload. Iron overload occurs in hemochromatosis and in transfusion hemosiderosis; it occurs as a result of prolonged excessive iron therapy and as a part of an interesting nutritional abnormality in Africa called cytosiderosis. The natives who develop cytosiderosis eat primarily a diet of maize cooked for long periods of time in iron pots. This cooking process, plus the Kaffir beer drunk by the natives, makes the iron content of the diet abnormally high, often more than 100 mg. per day. A few years ago Hegsted, Finch, and Kinney showed that rats fed maize also absorbed abnormally large quantities of iron. They made the interesting observation that the maize diet is low in phosphorus, and they postulated that there was, consequently, less of a tendency for the iron to be precipitated as insoluble phosphate salts in the intestinal tract.[14] The addition of phosphate to the experimental diet corrected the tendency for increased absorption.

The large amounts of iron in transfusion hemosiderosis are easy to understand, since every pint of blood contains from 0.2 to 0.25 gm. of iron. One hundred transfusions would provide the recipient with 20 to 25 gm. of the metal. Some workers have found at autopsy more than the expected amount of iron in the tissues of patients who had had frequent transfusions and have postulated that some of them must absorb iron at rates greater than normal, even though the tissues are overloaded. Definitive experiments to prove this have not been done.

In true idiopathic hemochromatosis, the increased amounts of iron have been something of a mystery. The iron must reach the body by absorption; but, while it is possible to demonstrate that some patients with hemochromatosis do absorb the metal at a rate greater than normal, others seem to have a normal rate of assimilation.[15] It has been suggested that the absorption is greater than normal until the late stages of the disease, when the tissues are so laden with iron that assimilation becomes retarded.[13] The mechanism of the increased absorption is unknown.

In hemochromatosis, the iron overload is frequently associated with fibrosis of the liver, diabetes, and evidence of myocardial damage. The question naturally arises as to how much of these associated changes is caused by a cytotoxic effect of the high iron concentrations. In the Bantu with cytosiderosis, diabetes is rare but hepatic cirrhosis is usually found. The cirrhosis in these cases may possibly be explained by other nutritional deficiencies. In transfusion hemosiderosis, diabetes develops in only a minority of patients, and cirrhosis, when it occurs, may possibly be the result of serum hepatitis, other infection, or prolonged hypoxia of the liver.

In our laboratory, dogs that received 0.5 to 1 gm. of iron per kilogram of body weight—amounts comparable to those found in hemochromatosis—are still well after six years.[16] They have no laboratory evidences of hepatic disease or of diabetes. Between 1945 and January, 1951, one of our patients with refractory or hypoplastic anemia received 587 transfusions containing well over 100 gm. of iron. He recovered, after splenectomy, and has received no transfusions during the past four years. He is well and has no diabetes nor any evidence of liver disease, although his skin is still bronzed.

There is reason to wonder if iron alone causes the cirrhosis and diabetes of hemochromatosis. Iron overload must be present, plus some unknown factor, to produce these changes. The unknown factor may be an associated metabolic disturbance or some intercurrent event responsible for liver damage, or it may be only time. Patients with hemochromatosis have iron overload over a period of many years. Patients with transfusion hemosiderosis usually receive transfusions because of diseases incompatible with long life. That iron is cytotoxic in high concentration is not denied. We wish merely to emphasize that other factors may play a pathogenic role in the production of abnormalities found in association with iron overload.

Summary

Nutritional factors are of major importance in the production or prevention of iron deficiency. Under some circumstances, when the intake is greatly increased, they can be responsible for iron overload. Healthy persons probably maintain a positive iron balance by a narrower margin than was formerly believed. Approximately 5 to 10% of the iron in food seems to be assimilated by normal adults; daily retention on a diet containing 12 to 15 mg. of iron, therefore, can be estimated to be about 0.6 to 1.5 mg. The amount of iron lost from the body each day in all ways except as blood seems to be between 0.5 and 1 mg. The requirements needed additionally by children and young women for growth and to compensate for menstrual flow place them in a precarious state of iron balance; poor diet or poor absorption can readily lead to the production of hypochromic anemia. In adult men or postmenopausal women, nutritional factors appear to be of less importance in the pathogenesis of iron deficiency. If purely nutritional iron deficiency ever occurs in these persons, many years would be required for its production. It is more likely that occult, intermittent bleeding, often difficult to detect, must also be present, along with inadequate diet or malabsorption, before severe degrees of iron deficiency develop.

One may conclude that for the normal child or the normal adult the recommendations of the Food and Nutrition Board for iron are adequate; however, they do not provide a wide margin of safety.

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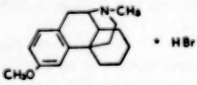
COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

Monographs and supplemental statements on drugs that appear in this column have been authorized by the Council for publication and inclusion in New and Nonofficial Remedies. They are based upon the evaluation of available scientific data and reports of investigations.

H. D. KAUTZ, M.D., *Secretary.*

Dextromethorphan Hydrobromide.—*d*-3-Methoxy-N-methylmorphinan hydrobromide.—The structural formula of dextromethorphan hydrobromide may be represented as follows:



Actions and Uses.—Dextromethorphan hydrobromide, a synthetic morphine derivative, is employed exclusively as an antitussive agent. Unlike codeine, dihydrocodeinone, and many of the other opium alkaloids used for this purpose, it exhibits little or no central depressant activity and does not produce analgesia. In addition, the drug appears to have no addicting effects, even after prolonged use in rather high doses. Its toxicity is low; side-effects reported to date have been slight, and there is some doubt that these can be attributed to the drug at all. The amount of bromine present in therapeutic doses is of no clinical significance.

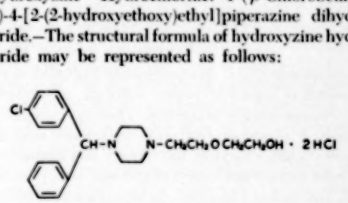
As with any antitussive drug, it is extremely difficult to obtain unbiased clinical data on effectiveness. With agents that have concomitant sedative actions, the possibility exists that patients become less conscious of and, hence, less bothered by cough although the actual frequency and intensity of cough is little affected. Dextromethorphan, however, has been subjected to well-controlled clinical evaluation. In a series of patients with severe chronic cough of varied etiology, dextromethorphan hydrobromide, codeine, and a placebo were administered under double-blind conditions; cough was rated numerically and recorded four times daily. The data obtained from a large number of such observations were subjected to a statistical analysis of variance. Only after the data had been thus analyzed was the identity of the medicaments revealed. These studies demonstrated that both dextromethorphan and codeine produced a definite and significantly greater diminution in cough than did the placebo. Thus, dextromethorphan hydrobromide compares favorably with the other antitussives used in clinical practice. Its activity in this respect is approximately as great as that produced by equal amounts of codeine.

Dosage.—Dextromethorphan hydrobromide is administered orally. The average dose for adults is 10 to 20 mg. one to four times daily. This dose is reduced to one-half for children over 4 years of age and to one-quarter for children under 4 years of age.

Preparations for use as stated for the foregoing drug are marketed under the following name: Romilar Hydrobromide.

Hoffmann-La Roche, Inc., cooperated by furnishing scientific data to aid in the evaluation of dextromethorphan hydrobromide.

Hydroxyzine Hydrochloride.—1-(*p*-Chlorobenzhydryl)-4-[2-(2-hydroxyethoxy)ethyl]piperazine dihydrochloride.—The structural formula of hydroxyzine hydrochloride may be represented as follows:



Actions and Uses.—Hydroxyzine hydrochloride, which is similar in chemical structure and pharmacological action to some of the antihistamines, produces depression of the central nervous system. Sedation is the most prominent action of hydroxyzine hydrochloride and forms the basis for its clinical use. The drug also appears to exert some actions similar to those of chlorpromazine; however, these are not sharply enough defined to permit pharmacological classification as a chlorpromazine-like drug.

Hydroxyzine hydrochloride has been employed clinically as a tranquilizing or calming agent for the symptomatic treatment of a wide variety of emotional or mental disorders characterized by anxiety, tension, and agitation; however, sufficient experience has not been gained to determine its ultimate usefulness as a psychotherapeutic agent. To date, its use in patients with frank psychoses has not been promising. The drug is likewise of little benefit in depressive states unless there is a strong overlay of agitation and anxiety. On the basis of currently available evidence, it would appear to be useful for the symptomatic management of neuroses rather than psychoses.

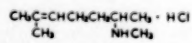
The toxicity of hydroxyzine hydrochloride is low. Drowsiness may occur shortly after the drug is taken but is transient and apparently never proceeds into true sleep. This effect, as distinguished from the tranquilizing action of the drug, seems to diminish in frequency and intensity upon prolonged administration.

Dosage.—Hydroxyzine hydrochloride is administered orally. The usual dose for adults is 25 mg. three times daily, but this may vary in amount and frequency according to severity of symptoms and individual response. For children between 6 and 12 years of age, doses of 10 mg. twice a day have been employed. This may be increased to 10 mg. three to four times daily if necessary. Sufficient experience is not available to state dosage requirements for infants or children under the age of 6.

Preparations for use as stated for the foregoing drug are marketed under the following name: Atarax Hydrochloride.

J. B. Roerig and Company, Division of Chas. Pfizer & Company, Inc., cooperated by furnishing scientific data to aid in the evaluation of hydroxyzine hydrochloride.

Isometheptene Hydrochloride.—2-Methylamino-6-methyl-5-heptene hydrochloride.—The structural formula of isometheptene hydrochloride may be represented as follows:



Actions and Uses.—Isometheptene hydrochloride, an unsaturated aliphatic amine, exhibits antispasmodic and vasoconstrictor properties. Thus, in experimental animals it produces relaxation of smooth muscle of hollow organs, including the urinary and gastrointestinal tract and the sphincters of the bile duct, pancreatic duct, and urinary bladder. Its antispasmodic effect on these structures is caused by stimulation of sympathetic (inhibitory) nerve endings rather than by inhibition of parasympathetic endings, as with atropine. The drug resembles epinephrine in that it produces moderate peripheral vasoconstriction, an increase in the contractile force of the myocardium, and a transient increase in blood pressure. Other effects include a slight bronchodilation, mydriasis, respiratory stimulation, and a shrinkage of nasal and pharyngeal mucosa. Isometheptene hydrochloride therefore may be classified as a sympathomimetic amine.

On the basis of these pharmacological studies, isometheptene hydrochloride has been employed clinically for the treatment of urinary tract spasm and spastic conditions of the gastrointestinal tract and its sphincters, as well as for the relief of migraine-like headache and other conditions believed to be caused by vasodilation in the cranial and cerebral vascular beds. Although it is the clinical impression of some physicians that patients with such conditions are benefited, convincing evidence is lacking to indicate that the drug, rather than the natural course of the disease, is responsible for alleviation of symptoms. Thus, the usefulness of isometheptene hydrochloride for relieving the pain of ureteral colic, as an aid in the passage of stone, for facilitating instrumentation during urologic or gastrointestinal examination, for relaxing gastrointestinal spasm, or for the alleviation of migraine or tension headache or histaminic cephalalgia is unsettled. Since pharmacological studies indicate that it may have some use in such conditions, and since it is of low clinical toxicity, its therapeutic trial may be justified in appropriate cases.

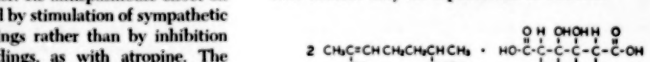
After parenteral administration of isometheptene hydrochloride, the most common side-effect is a rise in blood pressure, particularly in patients with a labile vascular system. This occurs much less frequently after oral administration. Other minor side-effects, which are rare and transient, include lightheadedness, nervousness, and sometimes nausea. The drug is contraindicated in all hypertensive patients. Initial parenteral administration should follow injection of a small test dose with subsequent careful checks on blood pressure.

Dosage.—Isometheptene hydrochloride is administered orally or intramuscularly. The usual oral dose for adults is 15 to 20 drops of a 10% solution (containing 100 mg. per cubic centimeter) every half hour for a total of four doses. By the intramuscular route, 50 to 100 mg. is injected for the control of acute pain in adults, but oral therapy should be substituted as soon as possible. The drug should never be injected intravenously.

Preparations for use as stated for the foregoing drug are marketed under the following name: Octin Hydrochloride.

Bilhuber-Knoll Corp. cooperated by furnishing scientific data to aid in the evaluation of isometheptene hydrochloride.

Isometheptene Mucate.—2-Methylamino-6-methyl-5-heptene mucate.—The structural formula of isometheptene mucate may be represented as follows:



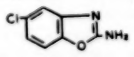
Actions and Uses.—Isometheptene mucate has the same actions and uses as the hydrochloride salt. (See the monograph on isometheptene hydrochloride.) Because it is not used by the parenteral route, it rarely causes hypertension.

Dosage.—Isometheptene mucate is administered orally or rectally. The usual oral dose for adults is 0.12 gm. every half hour for a total of four doses. Alternatively, one suppository containing 0.25 gm. may be inserted into the rectum; this procedure may be repeated in one hour if necessary.

Preparations for use as stated for the foregoing drug are marketed under the following name: Octin Mucate.

Bilhuber-Knoll Corp. cooperated by furnishing scientific data to aid in the evaluation of isometheptene hydrochloride.

Zoxazolamine.—2-Amino-5-chlorobenzoxazole.—The structural formula of zoxazolamine may be represented as follows:



Actions and Uses.—Zoxazolamine, a skeletal muscle relaxant, depresses or interrupts transmission of nerve impulses through polysynaptic pathways. Like mephenesin, its major sites of action are the brain stem, subcortical areas, and the spinal cord. Experiments with animals indicate that the drug has no direct effect on skeletal muscle, nor does it act at the myoneural junction. With experimental methods currently employed, comparatively little effect can be detected on monosynaptic arcs. Zoxazolamine has a longer duration of action than mephenesin and, in comparable dosage, its spasticity-reducing potency is greater. It likewise is more effective by mouth than mephenesin in equal amounts.

Zoxazolamine has been employed in a wide variety of conditions that may be unrelated in pathogenesis but in which either skeletal muscle spasm or spasticity is present as a common denominator. Of these disease entities, those resulting from musculoskeletal disorders, such as sprains, muscle strains and contusions, low back disorders, fibrositis, bursitis, myositis, and spondylitis, appear to respond best to the drug. A high percentage of patients with these conditions may be expected to be benefited by the drug with attending relief of muscle spasm discomfort. In such conditions, the drug should not be expected to bring about permanent improvement without appropriate attention to the application of suitable physical therapeutic measures. In patients with rheumatoid arthritis and osteoarthritis, the drug is of limited usefulness as an adjunct to salicylate and other forms of therapy. Although the drug may aid in the relief of muscle spasm, the concomitant production of muscular weakness in some cases can result in decreased over-all functional activity. The agent is of questionable usefulness in cervical root syndrome.

In general, patients with muscle spasm and spasticity resulting from musculoskeletal disorders appear to respond better to zoxazolamine than those with neurological disease. Of the latter category, beneficial results have been attained chiefly in patients with cerebral involvement, as for example, cerebral palsy and spastic paraplegia. Excluding those cerebral spastic states with athetoid derangements, the drug has been moderately successful in relieving hypertonus of the involved muscle groups in some patients. The more severe type of neurological spasticity states, namely those involving the spinal cord, have so far responded less well to zoxazolamine. These include such conditions as cord injury or neoplastic involvement and multiple sclerosis; results are likewise often disappointing in Parkinson's disease and various pyramidal tract lesions. The drug has no effect on basal ganglion disorders or convulsive diseases such as epilepsy.

Zoxazolamine has a margin of safety greater than that of mephenesin. Excessive muscle fatigue, which can occur after administration of both agents, is less pronounced after zoxazolamine. Side-effects to its administration, though frequent and often unpleasant, are not serious and are reversible upon withdrawal of the drug. The most frequent of these are nausea and vomiting; other less frequent side-effects include anorexia, headache, lightheadedness, transient skin rash, malaise, weakness, and drowsiness.

Dosage.—Zoxazolamine is administered orally. The usual dosage for adults is 0.25 to 0.5 gm. three or four times daily during meals or with food. For children, a dose of 0.25 gm. two to four times a day may be administered.

Preparations for use as stated for the foregoing drug are marketed under the following name: Flexin.

McNeil Laboratories, Inc., cooperated by furnishing scientific data to aid in the evaluation of zoxazolamine.

Additional Uses of Acetazolamide

The Council has evaluated the use of acetazolamide for the treatment of toxemia and edema of pregnancy, premenstrual tension, obesity, and drug-induced edema. This diuretic agent previously has been found useful for the management of cardiac edema, epilepsy, and glaucoma. On the basis of currently available evidence, the Council concluded that its oral administration to patients with toxemia and edema of pregnancy often will provide relief from the fluid retention that accompanies or characterizes mild preeclampsia of the third trimester. The drug is also useful for the treatment of the discomforts of premenstrual tension associated with fluid and electrolyte retention. Acetazolamide has been employed as an adjunct to dietary and other therapeutic measures for the management of simple obesity and excessive weight gain during pregnancy; preliminary results indicate a salutary effect in some patients. The drug also may be administered with phenylbutazone or cortisone to control the edema induced by these agents. The possibility of untoward effects from long-term use has not been assessed.

Acetazolamide is administered orally for all of the foregoing indications. Doses of 0.25 gm. daily are usual for the treatment of toxemia and edema of pregnancy. For premenstrual tension accompanied by fluid retention, doses of 0.25 gm. per day beginning 6 to 10 days prior to onset of menstruation or at the onset of symptoms have been employed; however, doses considerably lower than this may be adequate. The average dose for the adjunctive management of obesity is 0.25 gm. each day. When control of drug-induced edema is desired, doses of 0.25 gm. twice weekly may be tried.

The Council voted to amend New and Nonofficial Remedies to describe these additional uses of acetazolamide.

Lederle Laboratories Division, American Cyanamid Company, cooperated by furnishing scientific data to aid in the evaluation of these additional uses of acetazolamide.

Nuclear Radiations in the Treatment of Cancer.—Up to the present moment, investigations with only two radioactive isotopes have given us important therapeutic applications in hyperplastic and neoplastic diseases through selective localization. These are radiophosphorus in the treatment of polycythemia vera and radioiodine in the treatment of the thyroid hyperplasia of Grave's disease and in the palliative treatment of certain thyroid cancers. However, one who has worked in the field from the beginning and who is asked to sum up his experiences can't help saying that the therapeutic achievements have been disappointing; but even in the early days we believed that the greatest contribution of radioactive isotopes in the field of medical and cancer research would lie in tracer applications, and we have devoted most of our energies to the latter. Even though the achievements in prolongation of life and cures in cancer have not been great so far, one should not dismiss too lightly the contributions of artificial radioactivity and nuclear radiations in cancer therapy. The clinician should not underestimate the importance of relief from pain and extension of comfortable life, and here their value is well established.—J. H. Lawrence and C. A. Tobias, Radioactive Isotopes and Nuclear Radiations in the Treatment of Cancer, *Cancer Research*, March, 1956.

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AGING

Because of a progressive increase in the number of persons living beyond 60 years, more and more attention has been focused on the diseases to which they are especially prone and, more important, on ways of keeping them active and relatively healthy. In recognition of this, a Committee on Aging has been established in the A. M. A. Council on Medical Service (see this issue, page 210). Literally we start aging at the moment of conception and never stop until we die, but in the more usual sense aging starts when growth ceases. Lansing [1] defines aging as a process of unfavorable progressive change, usually correlated with the passage of time, becoming apparent after maturity and terminating in death. It is a gradual process, and Zimmerman [2] says that it represents a loss of functional reserve. One of the chief difficulties in studying this process is that no sure way is known at present to separate physiological sclerosis (the age-conditioned consolidation of tissues) from arteriosclerosis, to which it is not related histologically or pathogenetically. The concept that you are as old as your arteries does not get to the root of the matter, because aging is a process that can be recognized in plants and in animals that do not have arteries but in which a period of growth is followed by cessation of growth, decline, and death. Furthermore, Buerger and Hevelke [3] have shown that blood vessels in different organs age at different rates. Arteriosclerosis is also unevenly distributed in the body; thus the physiological process is masked by the pathological.

In man the main characteristics of aging are (1) tissue atrophy, the onset of which occurs at a different time and at different rates for different organs; as the oxygen supply to the tissues decreases the number and size of the cells also decreases; (2) gradual and partial replacement of more differentiated tissues by less differentiated tissue, e. g., hemopoietic tissue by fat in the marrow and interstitial fibrosis in various organs; and (3) deposition of pigment such as lipochromes in cells and of calcium in cartilage. Buerger and Hevelke studied the bradytrophic tissues, those tissues such as cartilage, crystalline lens, cornea, tympanic substantia propria, teeth, scar tissue, and the walls of the larger blood vessels, all of which have few if any capillaries. With age these tissues become dryer and denser. As their density increases, organic and inorganic inclusions appear and the tissue colloids become more concentrated. As these tissues become dryer, their nitrogen content decreases.

One of the questions regarding aging that is still unanswered is whether it is a property inherent in all living matter or whether it is related to physiological impairment in a specific organ or system such as the gonads. Shock [4] calls attention to the fact that all physiological processes do not deteriorate with age and cites examples: age induces no significant change in (1) the regulation of the acid-base equilibrium of the blood; (2) the fasting arterial blood sugar level (although there is an increase in the venous level); (3) the absorption of vitamin A; (4) the eosinophil response to corticotropin; or (5) the ability to retain nitrogen when given increased amounts of protein by mouth. Lansing believes that in senescence cellular permeability may be decreased due to an increase in the calcium content of the cell surface, but as yet there is no conclusive proof that this is the case. Shock has shown that with age there is a diminution in the renal plasma flow, loss of ability of the renal tubular cells to do osmotic work, and a decrease in the cardiac output at rest. Whether the changes that accompany aging are due to a reduction in the amount of active protoplasm in various organs or to reduced function of the protoplasm remaining is not known. In any case it has been shown that the aging of the blood vessels is accelerated by any increase in stress. Davidson [5] notes that elderly persons tend to lose interest in eating and that they eat foods high in carbohydrates and low in proteins, probably because these foods are easier to obtain, prepare, and chew, despite the fact that protein needs are not appreciably reduced with age. This may be a factor in accelerating the aging process.

One of the most important problems connected with aging is the determination of signs of mental deterioration, especially in business executives and persons in positions of responsibility. Birren [6] found that a test of writing speed differentiated more clearly between patients with senile psychosis and controls than did various combinations of standard mental tests. Flicker fusion tests at different levels of brightness showed a greater difference between old and young subjects as the level of brightness decreased. A battery of tests that would give a quantitative indication of the mental adaptability, judgment, and reasoning ability of aging executives could if properly used be of enormous benefit to business and to aging persons, many of whom are now forced to retire prematurely solely on the basis of their chronological age. Removal from positions of responsibility for signs of mental deterioration would also save companies from embarassment and should be a real service to the aging employee as well, freeing him in some cases to turn to a less taxing occupation and thereby prolonging his life.

1. Lansing, A. I.: What Is Aging?, Ludwig Kast Lecture, Bull. New York Acad. Med. **32**: 3-13 (Jan.) 1956.
2. Zimmerman, H. J., and others: Physiology of Aging, Illinois M. J. **109**: 251-254 (May) 1956.
3. Buerger, M., and Hevelke, G.: Do Human Beings Have Age of Their Blood Vessels? Angiology **7**: 137-151 (April) 1956.
4. Shock, N. W.: Some Physiological Aspects of Aging in Man, Bull. New York Acad. Med. **32**: 288-283 (April) 1956.
5. Davidson, C. S.: Protein Metabolism: With Particular Reference to Problems of Aging, Internat. Rec. Med. **167**: 428 (July) 1954.
6. Birren, J. E.: Changes in Speed and Timing, Pub. Health Rep. **70**: 844-846 (Sept.) 1955.

PANORAMA OF MEDICAL RESEARCH

Much favorable comment has been evoked by the appearance of the two volumes "Medical Research: A Midcentury Survey," published under the auspices of the American Foundation.[1] They spread before the reader an exciting picture of the achievements of the past 50 years, in the medical sciences alone. If one adds to this some conception of the activity that has gone on in mathematics, physics, chemistry, biology, the earth sciences, and the social sciences, the result is overwhelming. Turning from the accomplishments of the past to the tasks and opportunities of the future is equally inspiring. Is it possible that research in social sciences may lead to so good a knowledge of man, so thorough a control of his impulses, as to eliminate poverty and crime? Will the accumulating data of experimental psychology conquer war and insanity? Will sociology tell us at last how to ensure the peaceable utilization of nuclear energy? In particular, will the medical sciences provide the physician with more of the tools he needs to battle disability and pain?

The facilities for research of all kinds now provided by individuals, by industries, by universities, by foundations, by the federal government, and by other organizations have become enormous; the annual expenditures are stated in terms of billions of dollars. Millions are spent on the development of a single new synthetic fiber. Market surveys determine the most effective color schemes for food packaging, and acoustic engineers produce phonographs so realistic that the listener can imagine himself in the midst of a symphony orchestra during its most exalted moments. Photographs of the buildings devoted to research and development by one automobile manufacturing company—"Main Research Building, Service Building, Manufacturing Development Building . . . Engineering Building, Styling Building and Styling Auditorium Dome facing 22-acre lake"—form a sort of polychromatic nocturne of forms and reflections, and the area houses more than 4,000 "scientists, engineers, stylists and technicians . . . within its twenty-five modern air-conditioned buildings."[2]

It would appear that the resources of science and engineering are inexhaustible. From television in color to new forms of plastics, from pesticides to fertilizers, from house paints to lubricants, the engineer seemingly has but to formulate his wishes and the research laboratory translates them into substance. The structure of any organic compound seems to be capable of an infinitude of variations, and there are corresponding differences, if the compound has value as a drug, in its principal action and its side-effects.

The second volume of "Medical Research" reminds the reader of the principal unsolved problems of clinical medicine, especially cancer. There is an urgency about these medical problems that perhaps is lacking in many industrial problems—the fact that promptness or delay in a medical discovery makes so great a difference in human lives. For instance, in 1953 "108,405 infants in the United States died before their first birthday."[3] Although the rate of infant mortality has been whittled down from a figure of 101.0 per 100,000 in 1916 to 27.8 in 1953, there are still nearly 300 deaths each day of children under the age of one year. Similarly, there were 16,399 deaths from cirrhosis of the liver in 1953. Although this disease is 12th from the top in the list of causes of death in the United States, it is claiming nearly 45 lives each day.[4]

Sudden breaks in the mortality from particular diseases have occurred within the experience of every research worker whose memory goes back to the days before sulfanilamide and penicillin. In 1922, before the announcement of the discovery of insulin by Banting and Best, there was a widespread conviction among scientists that the problem of making good extracts of pancreas was on the verge of solution. One young woman, rapidly losing ground because of severe diabetes, sat in her wheel chair every day on the veranda of a famous research institution and watched two students pass on their way to the laboratory. One day as they passed she asked them weakly when they were going to make the discovery that would save her. Embarrassed by a sense of the insignificance of their own contribution, the two students never forgot her earnest question. And to their joy, even though the discovery of insulin was made in another laboratory, it did come in time to save this patient.

Medical research is distinguished not only by the sense of urgency that motivates it but also by the fact that it unites men against a common enemy. The impulse to share with others whatever information has been gained by research, and the need to do so, is probably more keenly felt in medicine than in other branches of science. This is illustrated, for instance, by the common use of multiple or second languages for summaries of important articles. The obligation to publish important medical results and the policy of disseminating them in other languages might be considered in some ways as a counterpart to the ethical principle that forbids a physician to purvey secret remedies.

Thus there exists the machinery, all oiled and primed, for producing research and distributing its benefits—gigantic machinery that has already produced wonderful things. There will come moments when it needs fresh programs to work on. No suggestion, however trivial or capricious, should be overlooked if it leads investigators in new directions. Manufacturers of drugs and apparatus are eager for suggestions from medical men. The Rockefeller Institute for Medical Research has sponsored a series of conferences between physicians and manufacturers of apparatus of various kinds. The fifth conference, for instance, held on February 21, 1956, dealt with electronic instrumentation in surgery. In connection with apparatus for surgical diathermy, a manufacturer remarked that there seemed to be no limit to what could be supplied in the way of current forms and strengths provided the requirements were sufficiently definite and the costs were within reason. Never before has humanity seemed so close to realizing the hope of seeing "alabaster cities gleam, undimmed by human tears."

1. Medical Research: A Midcentury Survey: vol. 1. American Medical Research: Its Principle and Practice; vol. 2. Unsolved Clinical Problems: Its Biological Perspective, published for American Foundation, Boston, Little, Brown & Company, 1955.
2. Saturday Evening Post, May 19, 1956, p. 9.
3. Infant Mortality: Each State and Territory, and Specified Possessions, 1953, Vital Statist.—Special Rep. 42:327 (Jan. 4) 1956.
4. Leading Causes of Death United States: Each State and Territory, and Specified Possessions, 1953, Vital Statist.—Special Rep. 42:302 (Dec. 27) 1955.

ORGANIZATION SECTION

A STATEMENT OF THE COMMITTEE ON AGING

At the June, 1955, session of the House of Delegates of the American Medical Association a resolution recommending the creation of a committee on geriatrics was adopted. As recommended, this committee was established under the Council on Medical Service. At the first meeting of the committee it became evident that the scope of its studies should be broader than the field inferred by the term geriatrics.

Unfortunately, geriatrics suggests the limited field of caring for the aged. It is a term that most serious students of aging avoid except to designate care of those far spent in their life content and activities. It probably has a certain utility but is not a stimulating title that can arouse the interest of members of the medical profession. After a thorough discussion, the committee recommended that its title be changed to that of Committee on Aging. This title was approved by the House of Delegates at the June, 1956, session.

Individuals, like institutions, may become obsolete—passé. Even then, these aged individuals have certain definite and important medical, housing, social, and emotional needs. Changes in the human body, in personality, and in social functions occurring as the individual grows and develops have introduced important new dimensions in medical science. As a result, problems of aging are multidimensional. As one national authority points out, these problems require not only a multiple disciplinary approach but also a correlating of diverse findings and planning for action. Information concerning the biological, psychological, and social processes bearing on the early years of human existence has increased our understanding of this period of human life. Control of the diseases, disorders, and deficiencies of the early years has created the opportunity for more and more individuals to live longer.

Gerontology concerns the scientific study of the phenomena of aging. All living matter changes with time in both structure and function, and the changes that follow a general trend constitute aging. Aging begins with conception and ends only with death. Growth, development, and maturation are thus a part of the aging process just as much as are atrophy and degeneration. The problems of gerontology extend from questions of changes in enzyme systems within individual cells to important social and economic problems of the interrelationships between aged people themselves and other members of society.

The medical profession has a unique opportunity, as well as an obligation, to study the medical, biological, psychological, and social aspects of growing older. Data concerning energy maintenance, fatigue control, and the preservation of specific motivation are needed. In the medical area the four most common disorders are (1) vascular deterioration, (2) cancer, (3) arthritis and rheumatism, and (4) mental disorders. Medical research should continue to study more and more the most common disorders of senior citizens.

Members of the medical profession should inform themselves of the great amount of study that has been devoted to problems of aging not only by physicians but also by sociologists, psychologists, social service workers, and political leaders. American medicine can play a practical and important part in enriching the lives of older citizens. Indeed, physicians should be expected to assume full leadership in all phases of this problem.

With some of these thoughts in mind the Committee on Aging has set forth the following objectives:

1. To explore problems concerned with the medical, biological, psychological, and social aspects of aging.

2. To collect data concerning energy maintenance, fatigue control, and the preservation of specific motivation.

3. To promote research in these areas.

4. To inform the medical profession of the availability of information regarding the aging process.

5. To stimulate medical society interest in the problems of aging.

6. To impress upon the practicing physician the important role he can play by assuming community leadership to enrich the lives of older citizens.

The members of the Committee on Aging are: Drs. Henry B. Mulholland, Chairman, Charlottesville, Va.; Edward L. Bortz, Philadelphia; Henry A. Holle, Austin, Texas; Wingate M. Johnson, Winston-Salem, N. C.; Theodore G. Klumpp, New York; Cecil Wittson, Omaha; and Frederick C. Swartz, Lansing, Mich.

HEALTH PLAN COMMISSION MAKES FIELD STUDIES

A subcommittee of the Commission on Medical Care Plans, appointed by the Board of Trustees of the American Medical Association in November, 1954, met in New York City June 29-July 1 to explore the possibility of conducting field studies of the many so-called independent plans having sponsors such as unions, management, and fraternal organizations. The committee members met with representatives of various medical societies to discuss local developments in

this particular area of medical service. Committee members also visited several union health centers, management-sponsored health centers, and a number of group practice units connected with the Health Insurance Plan of Greater New York. Additional visits and conferences of this type are being planned by the subcommittee, the members of which are Drs. H. Russell Brown, Watertown, S. D., Chairman; John F. Conway, Clovis, N. Mex.; F. J. Elias, Duluth, Minn.; and Leo Price, New York. Working with the subcommittee in New York was Dr. Leonard W. Larson, Bismarck, N. D., a member of the Board of Trustees and Chairman of the Commission on Medical Care Plans. The Commission filed a progress report at the A. M. A. Clinical Session in Boston, which appeared in the Dec. 3, 1955, issue of THE JOURNAL, page 1370.

INAUGURATION FILM AVAILABLE

A 30-minute film recording of Dr. Dwight H. Murray's inauguration as President of the American Medical Association is available for showing to medical society audiences. The high-quality Kinescope of a local telecast includes the induction ceremony, Dr. Murray's inaugural address, and the presentation of the 1956 Distinguished Service award to Dr. Walter L. Bierring. The presidential inauguration took place during the Annual Meeting in Chicago, June 12.

WORLD MEDICAL ASSOCIATION CONVENTION

PROVISIONAL AGENDA

10TH GENERAL ASSEMBLY

THE

WORLD MEDICAL ASSOCIATION

held at

Latin American Culture House

Ave. de Los Presidentes and Calle Tercera

Havana, Cuba

October 9-15, 1956

OPENING SESSION

October 10th at 10:00 A. M. (1000)

WELCOME TO DELEGATES

1. Call to Order and Welcome to Delegates by DR. KARL NIEDERBERGER (Austria), President.
2. Greetings:

RETURN OF DELEGATES

3. Receive: The list of delegates, alternate delegates and observers appointed by member associations and other bodies. (Doc 33.1/56)

STANDING ORDERS

4. Adopt: Standing Orders of The World Medical Association

AMENDMENTS TO ARTICLES AND BY-LAWS

5. Consider: Adoption of Paragraph II and III of By-Law 19 (Constitution and By-Laws)
6. Consider: Amendment to Article 5, subsection (ii) and By-Law 2 (Doc 32.2/56)

ELECTION AND INSTALLATION OF PRESIDENT

7. Elect: President for 1956-57
8. Install: President for 1956-57
9. Presidential Address

PRESIDING OFFICER

10. Consider: Desire of President relative to election of a Presiding Officer (By-Law 18; Doc 32.50/56).

Should the President desire to evoke By-Law 18 during the 10th General Assembly the following items should be considered.

11. Consider: Presidential Nomination of member of 10th General Assembly to preside over the business transactions of the Assembly;
12. Consider: Confirmation by General Assembly of President's Nomination;
13. Install: Presiding Officer

GREETINGS

14. Greetings: Extended by the President to the Observers of international and national organizations in attendance. (Due to limitation of time and heavy business agenda of the General Assembly, International and National Observers will not be able to address the Assembly at this time.
Organizations desiring messages extended to the 10th General Assembly are invited to transmit these to the Secretary General for inclusion in the Official Minutes.)

APPLICATION FOR MEMBERSHIP

15. Consider: Recommendations of the Council that applications of National Medical Associations approved by the Council be received into full membership in The World Medical

Association (Constitution and By-Laws, Articles 4 and 5; By-Laws 1, 2 and 15)
New Zealand Branch
British Medical Association) Doc 31.1/56

16. Receive: Delegates, and Alternate Delegates of New Member Associations.

MINUTES

17. Consider: Minutes of the 9th General Assembly held in Vienna, Austria, September 20-26, 1955, as compiled by the Secretary General and distributed (Doc 4.10/56) with the corrections received (Doc 4.10A/56)

ANNUAL REPORTS TO THE GENERAL ASSEMBLY

18. Consider: Annual Report of the Council to the General Assembly
Dr. Lorenzo Garcia-Tornel (Spain) Chairman of Council. (Doc 6.50/56)

19. Consider: Supplementary Report of the Council to the General Assembly (Doc 6.51/56)

20. Consider: Reports of Regional Secretaries

A. Asia — Dr. S. C. Sen (India) (Doc 7.10; 7.10A/56)

B. Australasia — Dr. J. G. Hunter (Australia) (Doc 7.20; 7.21/56)

C. Europe — Dr. P. Cibrie (France) (Doc 7.30/56C)

D. Latin America — Dr. Hector Rodriguez (Chile) (Doc 7.40; 7.40A/56)

21. Consider: Reports of Executive Editor and the Editorial Board of *World Medical Journal*, Dr. Austin Smith (USA) (Doc 9.1; 9.2/56)

22. Consider: Report of the Business Manager of *World Medical Journal*, Dr. Louis H. Bauer (USA) (Doc 9.10/56)

23. Consider: Annual Financial Reports
Reports of the Treasurer, Dr. Otto Leuch (Switzerland)

A. Financial Statement as of December 31, 1955 (Doc 5.1/56)

B. Closing of accounts of 1955 (Doc 5.2/56)

C. Auditors Report for 1955 (*World Medical Journal*, September 1956, Page 204)

D. Remarks of the Treasurer (Doc 5.3/56)

E. Tentative Budget for 1957 (Doc 5.5/56)

24. Receive: Annual Report of WMA Supporting Committees

A. United States Committee, Inc. (Doc 5.10/56)

B. Canadian Supporting Committee (Doc 5.50/56)

C. Report of other supporting Committees

25. Consider: Council Committee Reports;

A. Report of the Planning and Finance Committee, Dr. Otto Leuch (Switzerland) Chairman, (Doc 18.3/56)

B. Report of the Medical Education Committee, Sir Lionel Whitby (UK) Chairman (Doc 11.2/56)

C. Report of Miscellaneous Business Committee, Dr. Otto Rasmussen, (Denmark), Chairman (Doc 16.3/56)

D. Report of Medical Ethics Committee, Dr. P. Glorieux, (Belgium), Chairman, (Doc 17.-/56)

E. Report of International Liaison Committee, Dr. Jean Maystre, (Switzerland), Chairman (Doc 15.3; 15.4/56)

26. Consider: Report of Observers to other international organizations

A. Dr. Jean Maystre (Switzerland)—Official Liaison Officer
1. WHO (Doc 8.30; 8.30A/56)
2. ISSA (Doc 8.32; 8.33/56)
3. ILO (Doc)
4. others ( )

B. Dr. P. Cibrie (France)
UNESCO and CIOMS (Doc 8.10/56)

C. Dr. P. Glorieux (Belgium)
International Congress of Military Medicine and Pharmacy

GENERAL ASSEMBLY COMMITTEE

27. Consider: Report of the General Assembly Committee on Social Security (Doc 10.1/56)

28. Receive: Report on The Role of the Medical Profession in any Medical Care Plan.

A. The Status of the Profession in Social Security Schemes in Latin America, Dr. Hector Rodriguez (Chile) (Doc 10.2/56)

B. Freedom of the Medical Profession and Medical Care Plans, Dr. Rolf Scholegell (Germany) (Doc 10.3/56)

MOTIONS FROM MEMBER ASSOCIATIONS

29. Consider: Motions from Member Associations

SELECTION OF MEETING PLACE AND ELECTION

30. Consider: Confirmation of Selection of Istanbul, Turkey, as venue of 11th General Assembly in 1957.

31. Consider: Motion to approve Council recommendation of Venue for 12th General Assembly in Copenhagen, Denmark, in 1958.

32. Election: Elect

A. President-Elect 1956-57

B. Treasurer and Members of Council for three (3) years
Those whose terms expire in 1956 are:
Treasurer Dr. Otto Leuch (Switzerland)
Members of Council*
Dr. Lorenzo Garcia-Tornel (Spain)
Dr. Gunnar Gundersen (USA)
Dr. A. Mantellos (Greece)
*Dr. S. C. Sen (India)

*A regional vacancy exists in the Asiatic area and must be filled by a candidate from that area. The other three vacancies can be filled from any area.
(Doc 60.1; 60.2; 60.3; 60.4/56)

NEW BUSINESS

33. Consider: Any New Business

MINUTES

34. Consider: Motion that the Secretary General be empowered to prepare the Minutes of the 10th General Assembly for distribution subject to correction at the 11th General Assembly.

ADJOURNMENT

35. Consider: Motion for adjournment.

AGENDA

OF

SEVENTH ANNUAL CONFERENCE

OF

MEDICAL EDITORS

Latin American Culture House

Ave. de Los Presidentes and Calle Tercera

Havana, Cuba

October 11, 1956

9:30 A. M.–12:00 Noon

(0900–1200)

Chairman: Dr. Saturnino Picaza Del Pino
Director of Journal; *Annals of the Academy of Physical, Natural and Medical Sciences of Havana.*

Secretary: Dr. Austin Smith (USA)
Editor, *World Medical Journal* and *Journal of the American Medical Association.*

Subject: *Pan American Medical Publication Problems*

A cordial invitation is extended to all delegates, alternate delegates and observers to the 10th General Assembly to attend this meeting. The problems to be considered are not limited to Editors of Medical Publications, the practicing Doctor as the "Consumer" and "Contributor" to medical journals will be interested in the topics developed at this meeting.

I

LATIN AMERICAN PROBLEMS IN EDITING MEDICAL JOURNALS

by

Dr. Agustin Delachoix, h (Argentina)
Director: *Journal of the Argentina Medical Confederation*

Discussants: Dr. Ernst Fromm (Germany)
Hamburger Arzteblatt
Dr. Yasusaburo Sugi (Japan)
Journal of Japan Medical Association

General Discussion

II

THE SCIENTIFIC MEDICAL ARTICLE AND MEDICAL ETHICS

by

Dr. Rafael Lopez Ruiz (Colombia)
Editor: *Pan American Medical Confederation Journal*
Former Director: *Heraldo Medico*

Discussants: Dr. Felix Worré (Luxembourg)
Bulletin du Syndicat Medical
Dr. Viljo Rantasalo (Finland)
Finland Lakartidning

General Discussion

III

THE PAN AMERICAN CONFEDERATION JOURNAL AS A MEANS OF MEDICO-SOCIAL ADVANCEMENT IN LATIN AMERICA

by

Dr. Leopoldo E. Araujo (Cuba)
Editorial Board Member: *Pan American Medical Confederation Journal.*

General Discussion

IV

Consider: Any other business or discussion

V

Adjournment

LUNCHEON

A Luncheon, sponsored by the Nepera Chemical Company, Yonkers, New York, with Mr. Milton Lasdon as the Host will be held at the close of the meeting.
Participants in the Seventh Medical Editor's Meeting are invited to attend this Luncheon.

Reservations for the luncheon must be made in advance.

SCIENTIFIC PROGRAM

AT

10TH GENERAL ASSEMBLY

Latin American Culture House

Havana, Cuba

Friday, October 12, 1956

9:30 A. M.–1:00 P. M.

(0930–1300)

Chairman: Dr. Vicente Banet Pina
Professor of Clinicial Surgery, University of Havana.

I

SYMPOSIUM

PATHOLOGY IN PREMATURITY

A. *Causes of Death of the Premature in Cuba*

1. Dr. Emilio Soto Pradera
Member of the Cuban Pediatrics Society; Havana Society of Clinical Studies; American Academy of Pediatrics.

2. Dr. Federico Fuste Amieba
Pathologist, Obrera Maternity Clinic of Havana and Cuba Mental Hospital; Member of the Cuban Pediatrics Society.

3. Dr. Jose R. Montalvo
Member of the Cuban Pediatrics Society and the American Academy of Pediatrics.

B. *Infections of the Premature Infant*

1. Dr. Rene Montero De La Pedraja
Fellow–American Academy of Pediatrics

2. Dr. Carlos Montalvo Sotolongo
Professor of Pediatrics, University of Havana, School of Medicine; Staff Member–Havana Municipal Hospital for Children.

3. Dr. Jorge Beato Nunez
Instructor of Pediatrics, University of Havana, School of Medicine.

C. *Erythroblastosis and Kernicterus*

1. Dr. Serafin Falcon Lopez
Chief of Service of the Municipal Infants and Maternity Hospital of Havana "America Arias"; Member of the Cuban Pediatrics Society, the French Pediatrics Society and the American Academy of Pediatrics.

2. Dr. Julio Cornejo Gonzalez
Professor of Pediatrics at Our Lady of Mercy Hospital; Member of the Cuban Pediatrics Society.

3. Dr. Juan Bencomo Garcia
Chief of Blood Bank Municipal Maternity Hospital "America Arias" and Chief of Laboratories of General Pathology. Professor of Summer School at the University of Havana, School of Medicine.

4. Dr. Israel Borrajero
Pathologist, Municipal Maternity Hospital "America Arias," Havana.

D. *Hemorrhagic Disturbances of the Premature*

1. Dr. Angel A. Aballi Garcia Montes
Associate Professor, Faculty of Medicine, University of Havana; Member of Havana Society of Clinical Studies and Cuban Pediatrics Society.

2. Dr. Valeriano Lopez Banus
Staff Member, Infant and Maternity Division of University Hospital "General Calixto Garcia"

3. Dr. Sergio De Lamerens Zayas
Professor of Pediatrics, University of Havana, School of Medicine.

4. Dr. Israel Borrajero
Pathologist, Municipal Maternity Hospital "America Arias," Havana.

II

SYMPOSIUM

CARDIOVASCULAR SURGERY

A. *Cardiovascular Surgery in Cuba*

Professor Vicente Banet Pina, Past President–National Medical College; Professor of Clinical Surgery, University of Havana, School of Medicine; Member of Havana Academy of Physical, Natural and Medical Sciences.

B. *Tetralogy of Fallot*

1. Dr. Agustin Castellanos
Professor of Pediatrics, University of Havana; Director, Municipal Hospital for Children.

2. Dr. Angel Giral Casielles
Member of Executive Committee, National Medical College. Chief Surgeon, Cardiovascular and Chest Disease, Municipal Childrens Hospital.

C. *Pulmonary Stenosis*

1. Dr. Rodrigo Bustamante, M. R. C. P. (EDIN)
Cardiologist–University Hospital and "Lila Hidalgo" Hospital.

2. Dr. Armando Nunez Nunez
President–Cuban Angiology Society

D. *Inter-Auricular Communication*

1. Dr. Otto Garcia Diaz
Internist–Municipal Children's Hospital of Havana.

2. Dr. Antonio Rodriguez Diaz
Director—Institute of Cardiovascular and Chest Surgery.

E. *Mitral Stenosis*

1. Dr. Frank Barbera
Former Instructor, Temple University of Philadelphia; Chief—Department of Cardiology and Experimentation, Institute of Cardiovascular and Chest Surgery.

2. Dr. Hilario Anido
Chief Surgeon, Institute of Cardiovascular and Chest Surgery; Secretary National Society of Surgery.

F. *Anesthesia in Cardiovascular Surgery*

Dr. Francisco Gutierrez Pelaez
Anesthesiologist—Municipal Maternity Hospital "America Arias" and Cardiovascular Surgeon, Institute of Cardiovascular and Chest Surgery.

Travel Information

HAVANA, CUBA

Population: 674,376 Altitude: Sea level

Immigration: U. S. citizens require proof of nationality, round trip ticket or onward transportation, and documentation to country beyond Cuba.

Note: A passport is required of U. S. citizens who are racially Chinese. A smallpox certificate, not less than 8 days nor more than 3 years old, is required for return to the U. S.

General Information:

Language—Spanish. English is generally spoken by those in public activities. Special English-speaking police are on hand to help tourists.

Havana—The capital of Cuba, is a city of fun, sunshine and sociability.

Hotels—There are nine leading hotels in Havana, they are luxurious, beaches fine, food and drink among the best in the world. Everything is done to make your stay enjoyable. Almost all hotels have laundry and dry cleaning service.

Church—There are churches of nearly all major denominations, as well as a synagogue.

Climate—The temperature ranges from an average of 72° in January to an average high of 82° in July and August.

Currency—Monetary unit is the Peso—on a par with the U. S. dollar. Business travelers may take out of Cuba only $50.00 U. S. currency. All excess must be in travelers checks, money orders, etc.

Duty Free Imports—Tobacco, no restrictions—Cameras, no restrictions—Liquor, no restrictions.

AIR FLIGHTS

U. S. CARRIERS

PAN AMERICAN WORLD AIRWAYS

	Daily	Su	Daily	Daily	Mo-Fr	Daily	Mo-We Th-Sa	Su-Tu Fr	Daily
	Super 6	Super 6	Convair	Super 6	Convair	Super 6	Super 6	Super 6	Convair
Flight No.	411	505	413	415	513	417	434	436	421
Miami Lv.	8:00am	9:15am	10:00am	11:45am	1:00pm	3:00pm	5:00pm	5:00pm	7:15pm
Havana Ar.	9:00am	10:15am	11:07am	12:45pm	2:07pm	4:00pm	6:00pm	6:00pm	8:22pm

	Daily	Su-Tu Mo-Fr	Mo-Th Su	Daily	Daily	Daily	Tu-Th Su	Mo-Fr	Daily
	Convair	Super 6	Super 6	Convair	Super 6	Super 6	Super 6	Convair	Super 6
Flight No.	412	433	435	414	414	418	506	514	422
Havana Lv.	8:00am	9:45am	9:45am	11:45am	1:40pm	5:30pm	6:45pm	9:15pm	9:00pm
Miami Ar.	9:03am	10:45am	10:45am	12:45pm	2:40pm	6:30pm	7:45pm	10:18pm	10:00pm

DELTA AIRLINES

	Daily		Daily
Flight No.	751	Flight No.	750
New Orleans	Lv. 9:50pm	Havana	Lv. 3:00pm
Havana	Ar. 1:13am	New Orleans	Ar. 6:27pm

NATIONAL AIRLINES

	Daily		Daily		Daily (tourist)
Flight No.	451	Flight No.	351	Flight No.	501
New York	Lv. 5:30pm	Miami	Lv. 6:45pm	Miami	Lv. 2 pm
Havana	Ar. 8:50pm	Havana	Ar. 7:50pm	Havana	Ar. 2:50pm

	Daily		Daily		Daily
Flight No.	450	Flight No.	352	Flight No.	504
Havana	Lv. 10:30am	Havana	Lv. 11:30am	Havana	Lv. 4 pm
New York	Ar. 3:50pm	Miami	Ar. 12:35pm	Miami	Ar. 6:50pm

AIR FARE: ROUND TRIP

CHICAGO - HAVANA - CHICAGO

First Class		Tourist Class	
	$183.30		$136.60
Tax	18.32	Tax	13.66
	$201.52		$150.26

NEW YORK - HAVANA - NEW YORK

First Class		Tourist Class		30 Day Excursion (first class)	
	$180.00		$137.00		$146.50
Tax	18.00	Tax	13.70	Tax	14.65
	$198.00		$150.70		$161.15

MIAMI - HAVANA - MIAMI

First Class		Tourist Class	
	$36.00		$20.00
Tax	3.60	Tax	2.00
	$39.60		$22.00

MEDICAL NEWS

CALIFORNIA

Clinic Managers Conference.—University Extension and the School of Public Health at the University of California at Los Angeles, together with the National Association of Clinic Managers, are planning for the second clinic managers conference, Sept. 21-23 in Santa Barbara, with the Miramar Hotel as headquarters. Detailed programs may be had on request to offices of University of California Extension, Los Angeles 24.

Alcoholic Rehabilitation Commission.—Dr. David Frost, health officer for the city of Alameda since 1948, has been appointed director of the State Alcoholic Rehabilitation Commission. The commission will establish offices in the San Francisco Bay area. Under the new 1956-1957 budget of $704,798 (more than triple the $207,094 budget of the current fiscal year), the commission expects to expand its research, treatment, and rehabilitation programs and its information service. The commission is carrying out an intensive pilot program that involves (1) pure research into the problem of alcoholism; (2) pilot programs in one or two hospitals, where alcoholism will be considered as a medical problem; and (3) information service. The expanded program calls for the establishment of eight new pilot community alcoholic clinics (in addition to the project already in progress at the San Francisco Adult Guidance Clinic) at Los Angeles, San Diego, Sacramento, Alameda County, San Jose, Pasadena, Fresno, and Stockton. Dr. Frost, who has held a number of important committee appointments in the California Conference of Local Health Officers, is the newly elected president of the Northern California Public Health Association.

Postgraduate Lectures on Thursdays.—The Riverside–San Bernardino chapter of the American Academy of General Practice, in cooperation with the University of California at Los Angeles School of Medicine and University of California Extension, will hold a postgraduate medical lecture series on geriatrics, internal medicine, orthopedics, pediatrics, and surgery on the third Thursday in each month, Sept. 20-May 16, 1957, variously in San Bernardino, Upland, Riverside, and Fontana. Made possible by grant to the California Academy of General Practice from Wyeth Laboratories, Inc., the lectures are open to graduates of approved medical schools with consent of the planning committee. At the initial lecture, Sept. 20, 7 p. m. at the California Hotel in San Bernardino, Drs. Sherman M. Mellinkoff and Jack A. Cannon, Los Angeles, will lecture on pancreatitis. At the second lecture, Oct. 1 at the Mission Inn in Riverside, Dr. Sidney J. Cohen, Brookline, Mass., will discuss "New Drugs and Uses and Abuses of Steroids." All sessions include a 7 p. m. dinner meeting and a lecture period, 8-10 p.m. Requests for applications or information concerning the course should be made to Dr. Walter A. Sullivan, 108 "H" Street, Ontario (telephone 622-106), or Dr. Thomas H. Sternberg, Assistant Dean for Postgraduate Medical Education, University of California Medical Center, Los Angeles 24 (telephone GRanite 8-9711, ext. 202).

CONNECTICUT

Seminar in Psychiatry.—The 10th Connecticut Postgraduate Seminar in Psychiatry and Neurology will be presented Sept. 19, 1956–May 6, 1957 under the sponsorship of the department of mental health of the state of Connecticut and the department of psychiatry, Yale University School of Medicine, New Haven, in cooperation with the Institute of Living, Yale–New Haven Medical Center, U. S. Veterans Administration Hospital and Clinics, Connecticut State Hospital, Fairfield State Hospital, Norwich State Hospital, Mansfield State Training School and Hospital, and the Southbury Training School. Special seminar projects will include an Institute of Group Psychotherapy at Fairfield State Hospital, Newtown, Sept. 19, in which "Group Therapy of Psychoses" and "Clinical Review of a Chronic Schizophrenic Group" will be presented by Dr. Elvin V. Semrad, Newton, Mass., and "Problems in Working with Schizophrenics in Group Psychotherapy," by Dr. Christopher T. Standish, Boston. Both men will conduct workshops from 2 to 4 p. m. A symposium on research and practice will be held at the Institute of Living, Hartford, Oct. 18. "Evaluation of Pharmacodynamics and Hallucinogens" will be discussed by Dr. Max Rinkel, Boston (10 a. m. to 12 noon), and "Group Dynamics on the Ward: Patients and Personnel" by Dr. Alfred H. Stanton, Waverley, Mass. (1-3 p. m.). There are no fees for any of the courses, which include also basic neurology, pediatric neurology, clinical psychology, basic psychiatry, and child psychiatry. Copies of the program may be obtained from the Office of the Assistant Dean for Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar St., New Haven 11.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

DISTRICT OF COLUMBIA

Phi Delta Epsilon Lectureship.—The Beta Xi chapter of the Phi Delta Epsilon fraternity at the Georgetown University School of Medicine, Washington, D. C., will hold its third annual lectureship Sept. 28. The guest speaker, Dr. William Dameshek, director, Blood Research Laboratory, New England Center Hospital in Boston, will discuss "Polycythemia and Related Disorders."

ILLINOIS

Annual North Shore Lectures.—The seventh annual North Shore Health Resort lecture series will open Oct. 3 at 8 p. m. at the hospital (225 Sheridan Rd., Winnetka) with "The Unique Position of the Physician in Our Society" by Dr. Daniel Blain, clinical professor of psychiatry, Georgetown University School of Medicine, Washington, D. C. The American Academy of General Practice has approved these lectures for credit. The J. B. Lippincott Company of Philadelphia will publish the series as a book in 1957. All royalties that will accrue have been assigned to the American Psychiatric Association, of which Dr. Blain is medical director. Physicians and allied professional personnel are cordially invited to the lectures.

KENTUCKY

Society News.—The newly organized Kentucky chapter of Flying Physicians has named Dr. Marvin A. Bowers Jr., Louisville, president; Dr. J. Luther Fuller, Louisville, vice-president; and Dr. Homer B. Martin, Louisville, secretary-treasurer.

State Medical Meeting in Louisville.—The annual meeting of the Kentucky State Medical Association will convene in the Columbia Auditorium, Louisville, Sept. 17-20. The presidential address by Dr. J. Gant Gaither, Hopkinsville, will follow welcoming remarks by Dr. Irvin Abell Jr., Louisville, president, Jefferson County Medical Society, and the presentation of "The Problem of Arrhythmias in Cardiac Emergencies" by Dr. I. Frank Tullis, Memphis, Tenn., and "Salicylate Poisoning" by Dr. Katharine Dodd, Little Rock, Ark. Presentations by other out-of-state speakers will include:

Behavior and Gastric Secretion: Study of Infant with Gastric Fistula, Francis Reichsman, Rochester, N. Y.
Prosthetic Management of Palatal Deficiencies, Congenital and Acquired, Joseph B. Bustetter, D.D.S., Louisville.
Carcinoma of the Colon and Its Early Detection, Wendell G. Scott, St. Louis.
Present Status of Chemotherapy for Tuberculosis, Paul T. Chapman, Detroit.
Clinical Evaluation of the Rhinotomy Operation, John E. Bordley, Baltimore.
Treatment of Fractures in Children, J. Otto Lottes, St. Louis.
Early Diagnosis of Carcinoma of the Cervix, Francis L. McPhail, Great Falls, Mont.
Management of Urinary Tract Infections, Edgar Burns, New Orleans.

At the president's luncheon Wednesday, 11:50 a. m., Brown Hotel, Mr. William L. McGrath, Cincinnati, employer's delegate to the International Labor Organization, Geneva, Switzerland,

will speak on "Life Among the World Planners." The Kentucky Society of Anesthesiology will have as guest speaker Dr. Charles R. Stephen, Durham, N. C., who will discuss "Ventilation in Anesthesia." Dr. Louis A. Buie, Rochester, Minn., will consider "Office Practice in Proctology" before the Kentucky Academy of General Practice. The Kentucky Obstetrical and Gynecologic Society has scheduled a round table on obstetric difficulties, for which Dr. V. Edward Masters, Louisville, will serve as moderator. The scientific sessions will end Thursday afternoon with a panel discussion on upper gastrointestinal bleeding, moderated by Dr. Rudolf J. Noer, Louisville. An innovation at the annual meeting will be the presentation of scientific movies and of postgraduate refresher courses, including "The Management of Trauma," "Common Problems in Infants and Children," and "A Medical Symposium." The registration fee is $5. The woman's auxiliary will meet concurrently.

MASSACHUSETTS

Traineeships in Adolescent Care.—The Adolescent Unit at the Children's Hospital, 300 Longwood Ave., Boston 15, offers a general practice type of postgraduate training in the care of adolescents. A limited number of one-year traineeships are available to properly qualified physicians who have had two or more years of hospital experience after graduation from medical school. The teaching staff, including a gynecologist, endocrinologist, gastroenterologist, cardiologists, and psychiatrists, is directed by Dr. James R. Gallagher, to whom any inquiries should be sent.

Institute of Psychiatric Treatment.—The fourth annual Institute of Psychiatric Treatment will be presented in the Reception Building of the Boston State Hospital, Sept. 27-29, under the direction of Drs. Leo Alexander and Robert E. Arnot. Presentations by out-of-state speakers will include:

Ambulatory Treatment with Tranquilizing Drugs, Frank J. Ayd Jr., Baltimore.
Role of the Conditional Reflex in the Mechanism of Mental Illness and Therapy, W. Horsley Gantt, Baltimore.
Psychotherapy, Hans Lowenbach, Durham, N. C.
Demonstrations: Electric Sleep, Paul H. Wilcox, Traverse City, Mich.
Clinical Use of the New Drugs, Including Chlorpromazine and Reserpine, in the Major Psychoses, Nathan S. Kline, New York City.
Hypnosis (with clinical demonstration), Milton H. Erickson, Phoenix, Ariz.

Cocktails and dinner at the Harvard Club have been scheduled for 6:30 p. m. Friday. A review of experiences in organizing a treatment and research service at the Philadelphia State Hospital will be presented by Dr. Irving M. Rosen. The registration fee for the institute is $35. Further information may be obtained from Dr. Alexander at 433 Marlborough St., Boston.

MICHIGAN

Increase in Typhoid.—The Michigan Department of Health reports that the number of typhoid cases in Michigan is larger than at any time in the last 10 years. The number of cases in Michigan from January through Aug. 10 was 39, an increase of 24 over the same period in 1953 and the highest incidence since 1947. All typhoid cases reported in Michigan during 1956 have occurred in the lower peninsula, where they have been distributed evenly with no concentration by localities.

State Medical Meeting in Detroit.—The 91st annual session of the Michigan State Medical Society will convene Sept. 26-28 at the Sheraton-Cadillac Hotel, Detroit, under the presidency of Dr. William S. Jones, Menominee. On Wednesday, which has been designated General Practice Day, the following presentations will be made:

Perry S. MacNeal, Philadelphia, Diseases of the Adrenal Gland.
Francis R. Keating Jr., Rochester, Minn., Clinical Problem of Primary Hyperparathyroidism.
Seward E. Miller, Washington, D. C., The GP in Chronic Disease and Disabilities in Industry.
John K. Lattimer, New York, Chemotherapy of Renal Tuberculosis.
John P. Caffey, New York, Infantile Cortical Hyperostosis: Chronic and Prenatal Types.
Somers H. Sturgis, Boston, Psychosomatic Aspects of Gynecology.
Edwin J. DeCosta, Chicago, The Thyroid Gland in Pregnancy.
Otis L. Anderson, Washington, D. C., Chronic Disease, a Challenge to the Medical Profession.

The Thursday session will open with a surgical panel on thyroid diseases, moderated by Dr. Frederick A. Coller, Ann Arbor, with Drs. Dwight E. Clark, Chicago, E. Perry McCullagh, Cleveland, and James H. Means, Boston, as participants. Dr. G. Slaughter Fitz-Hugh, Charlottesville, Va., will then present "Indications for Tracheotomy" and Dr. John R. Schenken, Omaha, "The Cystic Ovary—Surgical or Nonsurgical?" After the William Beaumont, M.D., Annual Lecture, "Clues and Pitfalls in the Diagnosis of Jaundice," by Dr. Leon Schiff, Cincinnati, Dr. Theodore F. Schlaegel Jr., Indianapolis, will discuss "The Etiology and Diagnosis of Endogenous Uveitis"; Dr. Warren E. Wheeler, Columbus, Ohio, "Bacterial Disease in the Newborn"; and Dr. M. Ralph Kaufman, New York, "Psychotherapies in a General Hospital." The Friday assembly will hear the following papers:

LeRoy A. Calkins, Kansas City, Kan., Prolonged Labor.
Averill A. Liebow, New Haven, Conn., Some Aspects of Diagnosis of Lung Tumors and Cancer.
Herbert Rattner, Chicago, The Art of Topical Therapy.
Edward P. Cawley, Charlottesville, Va., Milkers' Nodules.
Kenneth E. Appel, Ardmore, Pa., Medical and Psychiatric Collaboration—Importance and Possibility.
O. Sidney Orth, Madison, Wis., Physician Alertness to Altered Physiology During Anesthetization.

Discussion conferences (12-1 p. m.) have been scheduled daily. They will be led Wednesday by Dr. Harold C. Mack, Detroit, Thursday by Dr. Frederick A. Coller, Ann Arbor, and Friday by Dr. Harold Henderson, Detroit. The general sessions will end Friday afternoon with a cross country panel on Cardiovascular Diseases, for which Dr. John M. Murphy, Detroit, will serve as moderator. Drs. Arthur C. Corcoran, Cleveland, George R. Meneely, Nashville, Tenn., Charles A. Poindexter, New York, and Myron Prinzmetal, Beverly Hills, Calif., will participate. On Wednesday at 6:30 p. m. the officers' night reception will precede the informal banquet, honoring officers of the Michigan State Medical Society and its woman's auxiliary. The president's annual address and the Andrew P. Biddle Lecture will be delivered that evening. The Michigan State Medical Assistants Society will meet Sept. 26-27 for a program that will include presentations by Dr. James D. Fryfogle, Detroit, ("Facts and Figments of Heart Surgery") and Dr. W. W. Bauer, Chicago, Director of the American Medical Association Bureau of Health Education ("Stop Annoying Your Patients"). The woman's auxiliary will meet concurrently with the parent organization.

MINNESOTA

Society News.—The Minnesota chapter of the Arthritis and Rheumatism Foundation recently named Dr. Cecil J. Watson, Minneapolis, president; Dr. Charles H. Slocumb, Rochester, vice-president; and Dr. John M. Wolff, Duluth, second vice-president.——The Twin City Radiological Society was recently organized by radiologists active in St. Paul and Minneapolis. The organization will hold quarterly meetings. Dr. Cyrus O. Hansen, Minneapolis, was elected chairman and Dr. Leo A. Nash, St. Paul, secretary.

NEW YORK

Society News.—Dr. Thurman B. Givan, Brooklyn, president-elect of the Medical Society of the State of New York, will be the principal speaker during the dinner at the annual meeting of the eighth district branch of the state medical society, Sept. 27 at the Bartlett Country Club, Olean. The scientific session, 2-5 p. m., will include the following presentations by guest speakers:

Cytologic Diagnosis of Malignancy, Thomas B. Simon, director of cytology, Memorial Center for Cancer and Allied Diseases, New York City.
The Tranquilizing Drugs, George B. Koelle, professor of pharmacology, University of Pennsylvania Graduate School of Medicine, Philadelphia.
The Surgical Risk in Patients with Cirrhosis of the Liver, Woodrow W. Lindenmuth, chief of surgical service, Veterans Administration Hospital, West Haven, Conn.

New York City

Visiting Professor of Physiology.—Dr. Jose del Castillo of London, England, has been appointed visiting professor of physiology at the State University of New York College of Medicine at New York City, Brooklyn, for one year, beginning on Sept. 1. A professor in the department of biophysics at University College, London, Dr. del Castillo has been on the faculties of the University of Salamanca, Spain; Middlesex Hospital Medical School, London; and the University of Bern, Switzerland.

Conference on Rehabilitation.—Rehabilitation of sick and injured workers will be the subject of a conference called by Miss Angela R. Parisi, chairman, New York State Workmen's Compensation Board, at the Sheraton-Astor Hotel, Sept. 27. Participants in the conference will include Dr. Paul H. Hoch, New York state commissioner of mental hygiene; Dr. Howard A. Rusk, director, Institute for Physical Medicine and Rehabilitation; Dr. Henry H. Kessler, director of the Kessler Institute, West Orange, N. J.; Assemblyman John Ostrander, chairman, joint legislative committee on industrial and labor conditions; Mr. Joseph Shaw, Associated Industries of the State of New York; and Mr. Thomas Jefferson Miley, president of the Commerce and Industry Association.

OHIO

Meeting of General Practitioners.—The sixth annual scientific assembly of the Ohio Academy of General Practice will be held in the new Franklin County Veterans Memorial Auditorium, Sept. 19-20. The banquet will be at the Deshler-Hilton Hotel Wednesday. Presentations by out-of-state speakers during the scientific sessions will include:

Trends in Pediatric, Adult, and Geriatric Nutrition, Thaddeus D. Labecki, Jackson, Miss.
Herniated Lumbar Intervertebral Disk Problem, Harold R. Oberhill, Chicago.
Abnormal Uterine Bleeding, Frederick H. Falls, Chicago.
Management of Congestive Heart Failure, E. Hugh Luckey, New York.
Cancer Detection in the Office of the Generalist, John S. DeTar, Milan, Mich.
Office Management of Leukorrhea, Leslie V. Dill, Washington, D. C.
Treatment and Prevention of Lateral Rotation of Legs and Flatfeet in Small Children, Joseph H. Kite, Atlanta, Ga.
Psychotherapy in General Practice, Vernon P. Williams, Boston.
Hypnosis for the General Practitioner, Seymour Hershman, Chicago.
Premalignant Lesions of the Rectum and Colon, Charles W. Mayo, Rochester, Minn.

RHODE ISLAND

Hospital Reunion.—The reunion of former interns, residents, and fellows of the Rhode Island Hospital, Providence, is scheduled for Sept. 28-29. Plans are being formulated for professional programs at the hospital on Friday morning and afternoon and on Saturday morning. The main social event will be a shore dinner at the Squantum Club for the homecomers and their wives.

VIRGINIA

Society News.—The Virginia Society of Ophthalmology and Otolaryngology recently elected Dr. L. Benjamin Sheppard, Richmond, president; Dr. Emanuel U. Wallerstein, Richmond, president-elect; Dr. Calvin T. Burton, Roanoke, vice-president; and Dr. Maynard P. Smith, Richmond, secretary-treasurer.

Personal.—At its annual meeting the Virginia Tuberculosis Association bestowed on Dr. Charles P. Cake, Washington, D. C., the Douglas Southall Freeman award for his efforts in tuberculosis control. Dr. Cake, who is president of the Southern Tuberculosis Association, is a past president of the Arlington County Medical Society, the Community Chest, Metropolitan Washington TB Conference, Virginia Trudeau Society, and the Swanson Parent-Teacher Association. During World War II he served as chief of the tuberculosis division, U. S. Public Health Service Hospital, Staten Island, N. Y.

Conference on Obstetrics and Gynecology.—The University of Virginia School of Medicine, Charlottesville, will have a Conference on Obstetrics and Gynecology Sept. 28. Guest speakers include Dr. Charles H. Mauzy, associate professor of obstetrics and gynecology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.; Dr. Robert A. Kimbrough Jr., chairman, department of obstetrics and gynecology, University of Pennsylvania Graduate School of Medicine, Philadelphia; and Dr. Andrew A. Marchetti, professor of obstetrics and gynecology, Georgetown University School of Medicine, Washington, D. C.

WASHINGTON

Symposium on Heart Disease.—The eighth annual Symposium on Heart Disease will be presented Sept. 28-29 at the University of Washington Medical School Auditorium in Seattle by the Washington State Heart Association and the Washington State Department of Health. The themes of the symposium, "Peripheral Vascular Disease" and "Congenital Heart Disease," will be developed in papers, panel sessions, and question periods by the following speakers: Drs. Frederic H. Bentley, Portland, Ore.; S. Gilbert Blount Jr., Denver; Denton A. Cooley, Houston, Texas; C. Walton Lillehei, Minneapolis; and J. Lowell Orbison, Rochester, N. Y. The symposium is in category I of the Academy of General Practice; credit can be earned hour for hour for attendance. There will be no registration fee. The Minnesota football game will be played at the University of Washington on Saturday.

WEST VIRGINIA

Hospital News.—Dr. Robert G. Blackwelder, Marion, Va., has been appointed superintendent of the Andrew S. Rowan Memorial Home at Sweet Springs, succeeding Dr. Edward E. Rose, formerly of Huntington, who resigned because of ill health. Dr. Blackwelder served as a member of the staff at Huntington State Hospital in Huntington from 1933 until 1939. Since October, 1954, he has been clinical director of the Southwestern State Hospital at Marion. He has also served as superintendent of the State Hospital at Raleigh, N. C., and of the Eastern Shore State Hospital at Cambridge, Md.

Society News.—Mr. Oliver Matthews, Kingwood, was recently elected president of the West Virginia Public Health Association; Dr. Bruce H. Pollock, Huntington, first vice-president; Mrs. Oletta M. Riffe, second vice-president; and Mrs. Katherine L. Brown, treasurer.——At the annual meeting of the West Virginia chapter of the American College of Surgeons Dr. Charles M. Scott, Bluefield, was elected president; Dr. Charles D. Hershey, Wheeling, vice-president; and Dr. Kenneth G. MacDonald, Charleston, secretary-treasurer.——The annual regional meeting of the West Virginia chapter of the American College of Physicians will be held at the Daniel Boone Hotel in Charleston, Sept. 29. The scientific session will open with "Acryoglobulin with Unusual Characteristics Associated with a Rare Hematological Disorder" by Dr. Edgar L. Crumpacker, Mary L. Petermann, Ph.D., and Dr. W. D. Irvine, the Greenbrier Clinic, White Sulphur Springs. It will close with "Coal Workers' Pneumoconiosis" by Dr. Peter P. Ladewig, pathologist, Laird Memorial Hospital, Montgomery. A cocktail party at 6 p. m. will precede dinner, 7 p. m., at the Edgewood Country Club. The guest speaker will be an officer of the American College of Physicians.

GENERAL

Conference on Occupational Therapy.—The 1956 conference of the American Occupational Therapy Association will be held Sept. 29–Oct. 5 at the Nicollet Hotel, Minneapolis. The theme of the conference will be "Time for Reflection," and the topics will include: Occupational Therapy in Relation to General Medicine and Surgery, Geriatrics, Pediatrics, Physical Disabilities, and Psychiatry.

Mid-Continent Psychiatric Association.—The Mid-Continent Psychiatric Association will hold its annual meeting at the Velda Rose Motel, Hot Springs, Ark., Sept. 21-23 under the presidency of Dr. Harold W. Sterling, North Little Rock, Ark. Members of the Arkansas Psychiatric Society will act as hosts. Speakers will include Dr. Nathan W. Ackerman, New York City; Dr. Ewing H. Crawfis, Cleveland; Dr. Leopold N. Judah, North Little Rock, Ark.; Dr. Jules H. Masserman, Chicago; Dr. Richard C. Proctor, Winston-Salem, N. C.; Drs. William G. Reese, Terry C. Rodgers, and William P. Kolb, Little Rock, Ark.; Dr. Martin L. Towler, Galveston, Texas; Dr. Jack P. Whisnant, Rochester, Minn.; and Dr. Charles D. Yobe, Hot Springs National Park, Ark.

Medical Writers Association Meeting in Chicago.—The American Medical Writers' Association will hold its 13th annual meeting at the Hotel Morrison, Chicago, Sept. 28 and its workshop

Sept. 29. Dr. Dwight H. Murray, Napa, Calif., President of the American Medical Association, will address the evening meeting, which will be preceded by a social hour (compliments of the Schering Corporation). Other speakers will include:

Austin E. Smith, Chicago, Role of an Official Journal.
Johnson F. Hammond, Chicago, The Make-Up of the J. A. M. A.
Mr. Gilbert S. Cooper, Chicago, Tables and Illustrations.
Mr. L. B. Murdock, Chicago, Problems of the Medical Manuscript Editor.
Morris Fishbein, Chicago, The Editorials of Medical Journals.
Harold Swanberg, Quincy, Ill., The A. M. W. A. Manuscript Editing Service.
Paul D. White, Boston, Experiences with Science Writers, Medical and Lay, and with the Press.
Alton Blakeslee, B.A., New York, Interpreting Medical Science for the Public.
Jonathan Forman, Columbus, Ohio, Workshops in Medical Writing for Medical Societies.
Sheldon O. Waife, Indianapolis, Problems and Prospects in Specialty Journal Editing.
Jacques P. Gray, Detroit, The A. M. W. A. Visiting Lectureship.

Mississippi Valley Medical Meeting.—The 21st annual meeting of the Mississippi Valley Medical Society will convene at the Hotel Morrison, Chicago, Sept. 26–28 under the presidency of Dr. Frank R. Peterson, Cedar Rapids, Iowa. The principal banquet speaker will be Dr. Dwight H. Murray, Napa, Calif., President of the American Medical Association. Also scheduled as banquet speakers are Dr. Wendell L. Downing, LeMars, Iowa, president, Iowa State Medical Society; Dr. F. Lee Stone, Chicago, president, Illinois State Medical Society; and Dr. Lien O. Simenstad, Osceola, Wis.; president, Wisconsin State Medical Society. Dr. Martin A. Seidell, Urbana, Ill., winner of the 1956 Mississippi Valley Medical Society essay contest, will present "A Compendium for Fluid and Electrolyte Management with Ordinary and Extraordinary Laboratory Facilities." The following panels will be offered:

Osseous Trauma—Fractures: Modern Concepts of Treatment (Samuel W. Banks, Chicago, moderator).
Gynecology (J. P. Greenhill, Chicago, moderator).
Thyroid Diseases (Arnold S. Jackson, Madison, Wis., moderator).
Recent Advances in Diagnosis and Therapy (John F. Sheehan, Chicago, moderator).
Arthritis and Rheumatic Disease (Charles H. Slocumb, Rochester, Minn., moderator).
Coronary Thrombosis (Paul D. White, Boston, moderator).

A cocktail party (courtesy of Chas. Pfizer & Co.) will precede, and the president's reception will follow the informal banquet.

Pediatricians Meet in New York.—The American Academy of Pediatrics will hold its 25th annual meeting at the Hotel Statler, New York, Oct. 6-11 under the presidency of Dr. Harry Bakwin, New York. Ten seminars have been scheduled for Saturday and Sunday and 20 round-table discussions for Monday through Wednesday. The general session will open Monday at 9:30 a.m. with a panel on obesity, moderated by Dr. Harry H. Gordon, Baltimore. Dr. Edith H. M. Lincoln, New York, will serve as moderator for a symposium on tuberculosis at 2 p.m. A symposium on genetics and disease (Dr. Barton Childs, Baltimore, moderator) will open the Tuesday morning session. On Wednesday morning, Dr. Paul R. Swyer, Toronto, Canada, will speak on hiatus hernia and Seymour Heymann, M.B., Johannesburg, South Africa, on the medical treatment of congenital hypertrophic pyloric stenosis. A panel discussion on adolescence will be presented Thursday morning (Dr. Waldo E. Nelson, Philadelphia, moderator). Thursday afternoon will be devoted to clinical sessions at various hospitals. The price of admission, $1.00, will include bus transportation from the Hotel Statler to the hospitals and return. The committee on adoptions has announced that its panel on adoptions Monday evening will be open to everyone interested in this discussion. The social program includes a special symphony concert at Hunter College Auditorium, Tuesday, 8:30 p. m.; a reception and cocktail hour (courtesy of Mead Johnson & Company) preceding the banquet Wednesday, 8 p.m.; an International Food Festival (Courtesy of Beech-Nut Packing Company) Monday and Tuesday; a welcome hour (courtesy Ross Laboratories) Sunday, 6-7:30 p.m.; breakfast (courtesy Libby's Baby Foods) Tuesday, 7-8:45 a.m.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States and its territories and possessions in the weeks ended as indicated:

Area	Aug. 18, 1956: Paralytic Type	Aug. 18, 1956: Total Cases Reported	Aug. 20, 1955, Total
New England States			
Maine	..	..	13
New Hampshire	..	..	41
Vermont	..	..	20
Massachusetts	2	9	448
Rhode Island	..	..	34
Connecticut	3	7	55
Middle Atlantic States			
New York	11	45	309
New Jersey	3	12	55
Pennsylvania	..	7	54
East North Central States			
Ohio	10	32	91
Indiana	21	34	23
Illinois	111	180	147
Michigan	21	62	94
Wisconsin	13	23	109
West North Central States			
Minnesota	2	16	62
Iowa	..	54	70
Missouri	7	21	13
North Dakota	1	2	5
South Dakota	..	3	3
Nebraska	1	7	23
Kansas	3	12	20
South Atlantic States			
Delaware	..	1	4
Maryland	2	2	23
District of Columbia	..	..	2
Virginia	8	13	27
West Virginia	4	7	9
North Carolina	13	23	43
South Carolina	2	11	21
Georgia	8	13	4
Florida	5	21	26
East South Central States			
Kentucky	3	15	36
Tennessee	5	14	20
Alabama	..	3	13
Mississippi	6	13	10
West South Central States			
Arkansas	8	11	10
Louisiana	19	36	16
Oklahoma	2	10	22
Texas	29	45	58
Mountain States			
Montana	..	2	9
Idaho	1	3	6
Wyoming	1	1	3
Colorado	6	11	17
New Mexico	3	6	5
Arizona	1	6	10
Utah	..	7	..
Nevada	..	..	1
Pacific States			
Washington	6	19	17
Oregon	4	7	11
California	43	65	71
Territories and Possessions			
Alaska	1	1	8
Hawaii	1	1	6
Puerto Rico	..	..	..
Total	390	804	2,148

Annual Clinical Conference.—The Kansas City Southwest Clinical Society will present its 34th annual Fall Clinical Conference Sept. 24–27 at the Municipal Auditorium, Kansas City, Mo. The fourth Edward Hohnan Skinner Memorial Lecture, "The Direction of Effort in Malignant Disease," will be delivered by Dr. Isidor S. Ravdin, Philadelphia, on the opening day. Other guest speakers and their first presentations include:

William A. D. Anderson, Miami, Fla., Tumors of Childhood.
R. Marden Black, Rochester, Minn., Continence-Preserving Procedures for Carcinoma of the Upper Rectum and Rectosigmoid.
George Crile Jr., Cleveland, Carcinoma of the Breast—the Surgeon's Dilemma.

Urban H. Eversole, Boston, Safeguarding the Surgical Patient.
Edgar Hull, New Orleans, Emergency Use of Corticoids and Corticotropins.
Chevalier L. Jackson, Philadelphia, What Can the Broncho-Esophagologist Do for the General Practitioner?
Laurance W. Kinsell, Oakland, Calif., Observations on Use of the Insulin-Sparing Sulfonamides.
John M. Lyon, Denver, Diagnostic and Treatment Suggestions in Psychoneurotic Reactions.
Walter G. Maddock, Chicago, Differential Diagnosis of Jaundice.
Carl V. Moore, St. Louis, Thrombocytopenic Purpura, Its Pathogenesis and Treatment.
LeRoy H. Sloan, Chicago, Bedside Neurology in Daily Practice.
E. Stewart Taylor, Denver, Cervical Carcinoma in Situ.
Don C. Weir, St. Louis, Accuracy and Limitations of Diagnostic Roentgenology.
Ben J. Wilson, Dallas, Texas, Treatment of Shock (Dangers and Complications of Nonspecific Therapy).

Panel discussions have been scheduled on Tumors of the Neck; Diagnosis and Management of Bone Disease; Recent Advances in Medicine and Surgery; Fluid and Electrolyte Balance; Common Types of Anemia; and Functional Gastrointestinal Disorders. Color television programs will be presented on Herniorrhaphy; Goiter Clinic; Caudal Anesthesia; Tracheotomy; Arthritis Clinic; Cesarean Section; Cholecystectomy; and Blood Transfusion. A clinical pathological conference is scheduled for Monday. Daily round-table luncheons have been scheduled with the distinguished guests. On Thursday Dr. Hubert M. Parker, Kansas City, Mo., will serve as moderator for a combined medical and surgical luncheon, closing with a panel discussion, "Recent Advances in Medicine and Surgery."

American Hospital Association.—The 58th annual convention of the American Hospital Association will be held at the International Amphitheatre in Chicago, Sept. 17–20. The Palmer House will be the headquarters hotel. The general sessions will open Monday afternoon with "What Are the Needs?" by Drs. Theodore G. Klumpp, New York, and Jack R. Ewalt, Boston. This presentation will be followed by "What Are the Resources?" by Dr. Lowell T. Coggeshall, special assistant for health and medical affairs to the Secretary of Health, Education, and Welfare, Washington, D. C., and Mr. George Bugbee, president, Health Information Foundation, New York. The president's reception and tea dance Monday, 6–9 p.m., will honor Dr. Albert W. Snoke, New Haven, Conn., president-elect. There is no charge, and everyone is welcome. At the federal luncheon Tuesday, 12:15 p.m., arranged for representatives of federal hospitals but open to all other convention registrants, the speaker will be Marion B. Folsom, Secretary, Department of Health, Education, and Welfare, Washington, D. C. Tickets are $3.50. The Conference on Hospital Planning Wednesday morning will be presented by the association in joint sponsorship with the American Association of Hospital Consultants, American Association for Hospital Planning, and American Institute of Architects. The general session Wednesday afternoon will be devoted to a program on "Meeting the Needs," which will have as participants Drs. Howard A. Rusk, New York, Joseph N. Schaeffer, Peoria, Ill., Leonard O. Bradley, Winnipeg, Manitoba, Canada, and Daniel Blain, Washington, D. C. At the banquet Wednesday evening, presentation of the distinguished service award to Dr. Charles F. Wilinsky, Boston, will follow presentation of honorary memberships to Dr. George F. Lull, Secretary-General Manager, American Medical Association, Chicago; Dr. Theodore G. Klumpp, chairman, Hoover commission task force on medical services, and president, Winthrop Laboratories, New York; and Emory W. Morris, D.D.S., president and general director, W. K. Kellogg Foundation, Battle Creek, Mich. A session on planning for disaster will be held at the Stock Yard Inn Thursday morning. The general sessions will end Thursday afternoon with a program on Hospital Professional Relations at which Dr. Dwight H. Murray, Napa, Calif., President of the American Medical Association, will speak for the physician.

FOREIGN

Congress of the History of Medicine.—The 15th International Congress of the History of Medicine will hold its biennial meet-in Madrid and Salamanca in Spain, Sept. 21–28. The provisional program lists the following papers: "American Indian Medicine in North America," "Daniel Le Clerc's Histoire de la Medicine," and "Iconography of the Frontispiece to the Fabrica." Further information may be obtained from the Secretaria General, Instituto Arnaldo de Villanova, Duque de Medinaceli, 4, Madrid, Spain.

CORRECTION

Diagnosis of Islet-Cell Tumors of Pancreas.—The last word in the second line of the second paragraph of the abstract on diagnosis of islet-cell tumors of the pancreas, in THE JOURNAL, July 28, page 1328, should have been "hypoglycemia" rather than "hyperglycemia."

EXAMINATIONS AND LICENSURE

AMERICAN BOARD OF ANESTHESIOLOGY: *Part I.* Various locations, July 19. Final date for filing application is Jan. 19. Sec., Dr. Curtiss B. Hickox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Oral.* St. Louis, Oct. 12-15. Final date for filing applications was April 1. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 15, 1956. Final date for filing application was May 1. *Oral.* New York City, Sept. 21-23. Final date for filing application was May 1. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.
Subspecialties. Cardiovascular Disease. Chicago, Nov. 30. Final date for filing application was June 1. *Gastroenterology.* Philadelphia, April 5-6. Final date for filing application is March 1.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTRETICS AND GYNECOLOGY: *Part I.* Various communities throughout the United States and Canada, Feb. 1. Candidates must submit case reports to the Office of the Secretary within 30 days of being notified of their eligibility to Part I. *Part II.* Chicago, May 16-25. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* St. Louis, Oct. 20-24. *Written.* Jan. 21. Final date for filing application was July 1. *Oral.* New York, May 23-27; Chicago, Oct. 7-11. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral. Part II.* Chicago, January 1957. Final date for filing application was Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Written and Oral.* Chicago, Oct. 8-11. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Written for Pathological Anatomy and Clinical Pathology,* Oct. 4-6. Final date for filing application was Sept. 1. Sec., Dr. Edward B. Smith, 1040-1232 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral. Part II.* New York City, Oct. 12-14, and San Francisco, Dec. 7-9. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Parts I and II.* New York City, June 8-9. Final date for filing application is March 1. Sec., Dr. Earl C. Elkins, 200 First St., S.W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY: Miami, Oct. 17-19. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Oral and Written. Public Health.* Philadelphia, Nov. 8-10. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore, Md.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, Sept. 29. Final date for filing application was Sept. 1. Sec., Dr. Stuart T. Ross, 320 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* New York, Dec. 10-11 and New Orleans, Mar. 18-19. Final date for filing application is Sept. 10. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Los Angeles, Sept. 30-Oct. 4. Final date for filing application was June 1. Tampa, April 1-6. Final date for filing application is Jan. 1. Washington, Sept. 23-28. Final date for filing application was June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I.* Various Centers Throughout the United States and in Certain Military Centers Abroad, Oct. 31. *Part II.* Buffalo, Sept. 24-25; Chicago, Oct. 15-16; New Haven, Nov. 19-20, Kansas City, Kan., Dec. 10-11; Los Angeles, Jan. 14-15; San Francisco, Jan. 17-18; Houston, Feb. 18-19; Nashville, Mar. 11-12; Boston, April 8-9, and New York, June 10-11.

AMERICAN BOARD OF UROLOGY: February 1957. Sec., Dr. William Niles Wishard, 1711 N. Capital Ave., Indianapolis 7.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, Sept. 7. Final date for filing applications was July 1. A subsequent written examination will be held in February 1957, and the closing date for registration is Dec. 1, 1956. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2.

DEATHS

Russell, Nelson Gorham ● Buffalo; born in New Market, Ontario, Canada, Aug. 26, 1872; University of Buffalo School of Medicine, 1895; joined the faculty of his alma mater as assistant in pathology, becoming assistant in medicine, professor clinical medicine, and professor of medicine; retired in 1937, on reaching his 65th birthday, and was named professor of medicine emeritus; specialist certified by the American Board of Internal Medicine; member of the American Association of Pathologists and Bacteriologists, American Clinical and Climatological Association, American Heart Association, American Association of the History of Medicine, American Trudeau Society, Society of Experimental Biology and Medicine, and the Buffalo Academy of Medicine; fellow and ex-governor of the American College of Physicians; veteran of the Spanish-American War; cited by General Pershing for "exceptionally meritorious and conspicuous services" during World War I; formerly chairman of the advisory health board; the Chancellor's medal of the University of Buffalo was presented to him on Feb. 22, 1945; in September, 1951, the annual bishop's award of the Episcopal Diocese of Western New York was presented to him for "outstanding service to the church"; the following year, at the annual dinner of the university's alumni board, received the Samuel P. Capen award for outstanding service to the university; consultant in medicine at the J. M. Adam Memorial Hospital in Perrysburg, Buffalo Columbus Hospital, and the Edward J. Meyer Memorial Hospital, where he formerly served as chairman of the board of managers; consulting physician and honorary vice-president and member of the board of trustees at the Buffalo General Hospital; died June 4, aged 83, of coronary occlusion.

Shepherd, Clara Sargent, Middleboro, Mass.; born in Valdosta, Ga., in 1889; University of Michigan Medical School, Ann Arbor, 1915; worked in the diabetic department at the Battle Creek (Mich.) Sanitarium; in 1919 went to China as the first woman physician to serve in the field of public health; worked with the National Council on Health Education, which was jointly sponsored by the Y. M. C. A. and the Y. W. C. A., and was on the faculty of the Women's College of Physical Education in Shanghai, which later became a department of Ginling Women's College in Nanking; for 20 years served as physician and public health director in the American Board of Missions at Shaowu and Foochow in Fukien; for a brief period was school physician at the Kuling American School; was evacuated from China just previous to Pearl Harbor, became health physician for the schools of Lansing, Mich., and later served as a physician on the staff of the outpatient department of Herman Kiefer Hospital in Detroit; retired from medical practice in 1952; assisted in writing textbooks on health for Chinese government schools and, with Dr. W. W. Peter, promoted public health campaigns in China's major coastal cities; died in St. Luke's Hospital July 1, aged 67, of cancer.

Davis, George G. ● Anchorage, Alaska; born in Chicago in 1879; Rush Medical College, Chicago, 1904; at one time associate professor of surgery at the University of the Philippines College of Medicine in Manila; served on the faculty of his alma mater and the University of Illinois College of Medicine in Chicago; during World War I served as honorary lieutenant colonel with the Royal Army Medical Corps and chief of staff of surgical service in the Third General Hospital in France; after the war practiced surgery in Chicago until 1943, when he went to Anchorage as chief of staff of the Alaska Railroad Hospital from 1943 to 1945; served as medical officer of the Alaska Native Service from 1945 to 1955; chief surgeon of the Carnegie-Illinois Steel Corporation in the Chicago area from 1919 to 1937; member of the House of Delegates of the American Medical Association in 1950; member of the founders group of the American Board of Surgery; member of the Western Surgical Association and the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; on the staff of the Providence Hospital in Anchorage; died April 21, aged 77, of cerebral hemorrhage.

● Indicates Member of the American Medical Association.

Cooke, Jean Valjean, St. Louis; born in Brownsville, Pa., June 19, 1883; Johns Hopkins University School of Medicine, Baltimore, 1908; instructor of pathology at the University and Bellevue Hospital Medical College in New York City from 1908 to 1910; instructor in pathology at the Tulane University School of Medicine, New Orleans, 1911-1912; from 1912 to 1917 associate in pathology and director of the laboratory at the University of California School of Medicine in San Francisco; professor emeritus of pediatrics at the Washington University School of Medicine, where he joined the faculty as assistant professor of pediatrics, later became associate professor and professor; specialist certified by the American Board of Pediatrics; during World War I served as consultant on epidemic diseases to the Secretary of War; member of the American Pediatric Society, which he served as president, and the Missouri State Medical Association; on the staffs of the St. Louis Maternity, St. Louis City, and St. Louis Children's hospitals; died in the Barnes Hospital June 29, aged 73, of lymphosarcoma.

Weld, Edward Howland ● Rockford, Ill.; born in Stillman Valley March 5, 1881; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1907; entered the Mayo Foundation in Rochester, Minn., in February, 1916, and left June 1, 1919; member of the House of Delegates of the American Medical Association 1947, 1948, and 1949; for 12 years councilor of the first district of the Illinois State Medical Society, which he later served as president; past-president and vice-president of the Winnebago County Medical Society; charter member of the American Geriatric Society; member of the American Urological Society and the Industrial Medical Association; on the staffs of the Rockford Memorial and St. Anthony hospitals; died in Mayo Clinic, Rochester, Minn., July 6, aged 75, of leukemia.

Greenman, Lawrence ● Pittsburgh; born in Brooklyn, N. Y., March 23, 1921; Yale University School of Medicine, New Haven, Conn., 1944; Renziehausen assistant professor of research medicine at the University of Pittsburgh School of Medicine; at one time on the faculty of his alma mater and Washington University School of Medicine in St. Louis; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; interned at the Grace-New Haven Community Hospital in New Haven, Conn.; served a residency at the Barnes Hospital in St. Louis, Grace-New Haven Community Hospital in New Haven, Conn., and the Presbyterian Hospital; on the staffs of the Children's Hospital, Presbyterian Hospital, and Woman's Hospital; died June 20, aged 35, of brain tumor.

Jones, William Harriman, Long Beach, Calif.; born in Battle Creek, Mich., in 1876; Cooper Medical College, San Francisco, 1899; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; past-president of the California Public Health Association; at one time associate professor of gynecology at the College of Physicians and Surgeons, medical department of the University of Southern California in Los Angeles; first health officer; instrumental in organizing the Seaside Memorial Hospital, where for years he was chief of staff; on the staffs of the Long Beach Community and St. Mary's Long Beach hospitals; founder and medical director of the Harriman Jones Clinic and Hospital, where he died June 17, aged 80, of coronary occlusion.

Guedel, Arthur Ernest, Los Angeles; born in Cambridge City, Ind., June 13, 1883; Indiana University School of Medicine, Indianapolis, 1908; emeritus associate clinical professor of surgery (anesthesiology) at the University of Southern California

School of Medicine; specialist certified by the American Board of Anesthesiology; member of the American Society of Anesthesiologists; veteran of World War I; from 1920 to 1928 lecturer on anesthesiology at his alma mater; for many years on the staffs of the Indianapolis General, St. Vincent's, and Protestant Deaconess hospitals in Indianapolis; served on the staffs of the Cedars of Lebanon, Queen of Angels, and California hospitals, and the Methodist Hospital of Southern California; died June 10, aged 72, of arteriosclerotic heart disease.

Wear, Thomas Ralph ● Tuscaloosa, Ala.; born in Haleyville, Feb. 23, 1917; Washington University School of Medicine, St. Louis, 1942; interned at the Employees' Hospital of the Tennessee Coal, Iron and Railroad Company in Fairfield, Ala.; formerly a resident at the Regional Hospital (U. S. Army) Aviation Cadet Center, San Antonio, Texas; veteran of World War II; practiced in Hamilton, where he was vice-president of the Marion County Medical Society, trustee of the local school board, and county health officer; on the staff of the Bryce Hospital; member of the American Academy of General Practice; died in the Wilson Hospital in Haleyville June 23, aged 39, of lymphocytic leukemia.

Capell, Clarence Swift ● Kansas City, Mo.; born in Marietta, Ohio, Nov. 14, 1874; John A. Creighton Medical College, Omaha, 1902; specialist certified by the American Board of Urology; member of the American Urological Association and the Kansas City Southwest Clinical Society; past-president of the Jackson County Medical Society; president of the Kansas City Urological Society, 1954-1955; veteran of World War I; served as chief and president of the staff, St. Mary's and St. Joseph hospitals; for many years director and chief of the urologic service, Kansas City General Hospital; died June 24, aged 81, of coronary arteriosclerosis.

Hammond, Robert Bertine, Bradenton, Fla.; born in Amenia, N. Y., Feb. 3, 1883; Long Island College Hospital, Brooklyn, N. Y., 1908; member of the Medical Society of the State of New York and the American Society of Anesthesiologists; fellow of the American College of Anesthesiology, of which he was a founder; past-president of the American Regional Society of Anesthesiologists, New York Society of Anesthetists, and the Eastern Society of Anesthesiologists; an associate member of the American Medical Association; specialist certified by the American Board of Anesthesiology; for many years practiced in White Plains, N. Y.; served on the staffs of the Grasslands Hospital in Valhalla, N. Y., the St. Agnes Hospital in White Plains, N. Y., and the White Plains (N. Y.) Hospital, where he died May 31, aged 73, of arteriosclerosis.

Neilson, John Land ● Captain, U. S. Navy, retired, Washington, D. C.; born July 31, 1880; Harvard Medical School, Boston, 1902; appointed assistant surgeon in the Navy in 1902; during his career of 43 years, served as commanding officer of naval hospitals in Guam, San Diego, Pearl Harbor, and Mare Island; served in the Philippines and Guam, at the Naval Training Station at Newport, R. I., at Mare Island, and aboard the USS Buffalo; served in the office of the Navy surgeon general, as flag surgeon of the U. S. Pacific Fleet, Destroyer Force, and aboard the USS California, and as a member of the Navy Retirement Board in Washington; retired Jan. 1, 1943; fellow of the American College of Surgeons; died June 14, aged 75, of myocardial infarction.

Kaufman, Charles J. ● Castle Point, N. Y.; born in Brooklyn, N. Y., Jan. 29, 1897; Cornell University Medical College, New York City, 1921; served on the faculty of his alma mater; formerly associate professor of medicine (tuberculosis) at the University of Colorado School of Medicine in Denver; member of the American College of Chest Physicians and the American Trudeau Society; at one time medical director of the National Jewish Hospital in Denver and on the staffs of the Sea View Hospital in Staten Island and the Metropolitan Hospital in New York City; chief, tuberculosis service, Veterans Administration Hospital; died in the Presbyterian Hospital, New York City, June 15, aged 59, following a prostatectomy.

Singer, Karl ● Chicago; Medizinische Fakultät der Universität, Vienna, Austria, 1927; specialist certified by the American Board of Internal Medicine; member of the Association of American Physicians; fellow of the American College of Physicians; at one time associate in physiology at his alma mater; served on the faculty of Tufts College Medical School in Boston, where he was a research fellow at the Beth Israel and Joseph H. Pratt Diagnostic hospitals; since 1947 director of the hematology department at the Michael Reese Hospital, where he died July 12, aged 54, of bronchopneumonia and carcinoma of the lung.

Abner, John W., Atchison, Kan.; Eclectic Medical University, Kansas City, Mo., 1914; died June 8, aged 88, of chronic aortitis.

Amos, William Frederick, Portland, Ore.; Willamette University Medical Department, Salem, 1890; Columbia University College of Physicians and Surgeons, New York City, 1892; at one time on the faculty of the University of Oregon Medical School; served as secretary of the Oregon State Medical Society; at one time an associate editor of *Medical Sentinel;* died June 25, aged 86.

Anderson, Raymond Ravenel, Jersey City, N. J.; Howard University College of Medicine, Washington, D. C., 1930; died in the Jersey City Medical Center June 22, aged 54.

Anderson, Richard Speight ● Whitakers, N. C.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1924; veteran of World War II; for many years on the staff of the Rocky Mount (N. C.) Sanitarium; died in the Edgecombe General Hospital, Tarboro, June 6, aged 57.

Anrode, Ralph Austen ● Davenport, Iowa; Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia, Germany, 1920; on the staffs of the Mercy Hospital and the St. Luke's Hospital, where he died June 29, aged 65, of coronary occlusion.

Armstrong, Frederic Clinton ● Cascade, Iowa; John A. Creighton Medical College, Omaha, 1920; member of the American Academy of General Practice; veteran of World War I; died in the Veterans Administration Hospital, Iowa City, June 30, aged 61, of carcinoma of the lung with metastasis to the kidney.

Avery, Hiram Henry, Omaha; Kansas City (Mo.) Hahnemann Medical College, 1914; veteran of World Wars I and II; died in the Veterans Administration Hospital May 17, aged 65, of ruptured aortic aneurysm.

Bailey, Thomas B., Marshall, Texas; Baylor University College of Medicine, Dallas, 1916; died in the Kahn Memorial Hospital June 22, aged 71.

Bang, Sarah Allen, Havertown, Pa.; Temple University School of Medicine, Philadelphia, 1906; died in the Doctors Hospital, Philadelphia, June 15, aged 86, of ovarian tumor.

Barber, Edna Mabel, Alameda, Calif.; Oakland (Calif.) College of Medicine and Surgery, 1914; an associate member of the American Medical Association; died June 20, aged 71, of melanotic carcinoma with metastases.

Barber, William Jefferson ● Butler, Ala.; Tulane University of Louisiana School of Medicine, New Orleans, 1929; member of the American Academy of General Practice; medical superintendent and owner of the Barber Hospital; died in the Jefferson-Hillman University Hospital, Birmingham, June 11, aged 49, of obstructive jaundice and pancreatitis.

Barnes, Robert Wallace, Dallas, Texas (licensed in Texas under the Act of 1907); died June 19, aged 87.

Barnett, Thomas Rowland ● Hillsboro, Texas; Baylor University College of Medicine, Dallas, 1926; member of the American Academy of General Practice; part owner of the Hillsboro Clinic-Hospital, where he was director of the staff, and where he died June 21, aged 57, of coronary occlusion.

Beare, John William ● Chester, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1907; member of the board of health of Chester; on the staffs of St. Clement's Hospital in Red Bud and St. Andrew's Hospital in Murphysboro; died June 23, aged 75, of arteriosclerotic heart disease with coronary thrombosis.

Berke, Samuel David ● Indio, Calif.; Dalhousie University Faculty of Medicine, Halifax, Nova Scotia, Canada, 1926; veteran of World War II; on the staffs of the Casita and Coachilla Valley hospitals; died in the Veterans Administration Hospital, Los Angeles, June 5, aged 52, of bronchiectasis and cor pulmonale.

Berry, Joseph Alonzo ✱ Tuskegee, Ala.; Rush Medical College, Chicago, 1925; fellow of the International College of Surgeons; member of the American Society for Surgery of the Hand; on the staff of the Veterans Administration Hospital; died in New York City June 13, aged 60, of aortic aneurysm.

Bilstad, Gunerius Ellsworth, Cambridge, Wis.; Northwestern University Medical School, Chicago, 1898; died June 26, aged 82, of arteriosclerotic heart disease.

Binder, Israel ✱ Philadelphia; Medico-Chirurgical College of Philadelphia, 1911; member of the American Academy of Pediatrics; on the staff of the St. Luke's and Children's Medical Center and the Olney Hospital and Lawncrest Diagnostic Clinic; died in Panama City, Fla., June 11, aged 65.

Blackburn, Cecil Howell ✱ Conyers, Ga.; Washington University School of Medicine, St. Louis, 1941; member of the Medical Association of the State of Alabama; died June 4, aged 46.

Bostick, John Benton ✱ Lieut. Commander, U. S. Navy, retired, Fresno, Calif.; College of Physicians and Surgeons of San Francisco, 1913; entered the U. S. Navy July 20, 1921; retired Sept. 1, 1939; veteran of the Spanish-American and World Wars; died June 6, aged 80, of cerebral vascular thrombosis.

Boswell, Harry Dillman ✱ Henryetta, Okla.; Northwestern University Medical School, Chicago, 1912; died in the Haynes Hospital July 4, aged 73, of pneumonia and heart disease.

Breitenbach, Lawrence Prell, Detroit; Detroit College of Medicine, 1911; formerly on the faculty of his alma mater; served on the staff of St. Mary's Hospital; died June 12, aged 74, of arteriosclerosis.

Briggs, George Abiel ✱ Sacramento, Calif.; Medical Department of the University of California, San Francisco, 1905; served overseas during World War I; past-president of the Sacramento Society for Medical Improvement; fellow of the American College of Surgeons; one of the founders, member of senior staff, and for many years secretary-treasurer of the board of trustees of the Sutter General Hospital, where he died June 10, aged 73, of carcinoma of the prostate with metastases.

Brown, John Charles, New York City; Albany (N. Y.) Medical College, 1892; died in St. Luke's Hospital June 14, aged 85, of pneumonia.

Bryan, William Juel, Jr. ✱ Tulsa, Okla.; Baylor University College of Medicine, Dallas, Texas, 1921; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Diabetes Association; on the visiting staff of the St. John's Hospital; on the staff of the Hillcrest Medical Center, where he served on the governing board and later was named honorary board member; died July 4, aged 60, of cancer.

Bryant, Arthur Ralph, Beatrice, Neb.; Rush Medical College, Chicago, 1930; an associate member of the American Medical Association; past-president of the Gage County Medical Society; veteran of World War II; on the staffs of the Mennonite Deaconess Home and Hospital and the Lutheran Hospital, where he died June 15, aged 52, of pinealoma.

Budaeff, Ivan Titus ✱ Daly City, Calif.; University of Oregon Medical School, Portland, 1930; member of the American Academy of General Practice; died June 12, aged 60, of carcinoma of the lung with metastasis.

Bussey, Benjamin Peyton, Cairo, Ga.; Medical College of Georgia, Augusta, 1954; interned at the Charity Hospital of Louisiana in New Orleans, where he served a residency; killed June 29, aged 28, in a plane crash.

Butler, Henry Anderson ✱ Liberty, Miss.; University of Tennessee College of Medicine, Memphis, 1934; died July 4, aged 57, of heart disease.

Byrd, Emmett Earl ✱ Jonesboro, Tenn.; Lincoln Memorial University Medical Department, Knoxville, 1912; veteran of World War II; served as director of the Washington County Health Department; retired from the Veterans Administration May 31, 1950; died in the Memorial Hospital, Johnson City, April 23, aged 65, of coronary disease.

Campbell, Clarence G., New York City; Bellevue Hospital Medical College, New York City, 1890; died June 16, aged 88, of bronchopneumonia, arteriosclerotic heart disease, and generalized arteriosclerosis.

Clarke, James Cunningham ✱ La Grange, Ill.; Rush Medical College, Chicago, 1913; fellow of the American College of Surgeons; on the staffs of the Community Memorial General Hospital and the Hinsdale (Ill.) Sanitarium and Hospital, where he died July 12, aged 70, of a heart attack.

Cooper, Jesse Robert ✱ New Castle, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1894; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, and the American College of Radiology; veteran of World War I; on the staff of the New Castle Hospital; died in the Jameson Memorial Hospital June 14, aged 84, of cerebral hemorrhage.

Darrah, John Russell ✱ Colonel, U. S. Army, retired, Amarillo, Texas; University of Nebraska College of Medicine, Omaha, 1935; certified by the National Board of Medical Examiners; veteran of World War II; retired from the regular Army June 18, 1955; died June 6, aged 48.

Douglass, Henry Francis, Washington, D. C.; Howard University College of Medicine, Washington, D. C., 1938; interned at the Freedmen's Hospital, where he served a residency; died suddenly June 7, aged 42, of a heart attack.

Engel, Henry ✱ Dover, Ohio; Ludwig-Maximilians-Universität Medizinische Fakultät, München, Bavaria, Germany, 1907; died in the Mercy Hospital, Canton, June 3, aged 74, of infection following prostatic operation.

Farley, William Chase ✱ Methuen, Mass.; Medical School of Maine, Portland, 1893; Hahnemann Medical College and Hospital of Philadelphia, 1894; on the courtesy staff of the Lawrence (Mass.) General Hospital; died June 14, aged 86, of intestinal and gastric carcinoma.

Freedman, Theodore Raphael, Far Rockaway, N. Y.; New York Homeopathic Medical College and Flower Hospital, New York City, 1929; member of the Medical Society of the State of New York; died in St. Joseph's Hospital, New York City, June 18, aged 52, of pulmonary embolism and infarction, myocardial infarction, and coronary sclerosis.

French, William Oscar ✱ Honolulu, Hawaii; Stanford University School of Medicine, San Francisco, 1926; served in France during World War I; in 1924-1925 was in the U. S. Army Reserve, from 1926 to 1928 in the regular Army, and from 1928 to 1932 in the National Guard; died April 11, aged 60.

Frey, Joseph Louis Edward ✱ New York City; Georgetown University School of Medicine, Washington, D. C., 1907; died July 6, aged 71, of general and coronary arteriosclerosis.

Hankey, Stacy Marlin ✱ Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1903; specialist certified by the American Board of Urology; member of the American Urological Association; on the staffs of the Veterans Administration Hospital and the Passavant Hospital, where he died June 21, aged 82, of carcinoma of the stomach.

Hester, William Lee ✱ Lubbock, Texas; Southern Methodist University Medical Department, Dallas, 1914; associated with the Regional Veterans Administration; died in St. Mary of the Plains Hospital in Lubbock May 30, aged 65, of bronchogenic carcinoma with cerebral metastasis.

Heyman, Ernest Fred ✱ Red Bank, N. J.; Universität Leipzig Medizinische Fakultät, Saxony, Germany, 1923; died in the Monmouth Memorial Hospital, Long Branch, May 7, aged 55, of carcinoma of the prostate.

Hildebrand, William Owen ✱ Topeka, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1905; died in the Elkhart (Ind.) General Hospital June 1, aged 80, of acute coronary occlusion.

Jenkins, Bertha Elizabeth, Oakland, Calif.; Oakland College of Medicine and Surgery, 1919; an associate member of the American Medical Association; died May 22, aged 70.

Kirkland, Benjamin Franklin, Long Beach, Calif.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1898; formerly member of the city council; died May 24, aged 86.

Komisar, Paul Stanislaw ✱ Erie, Pa.; Tufts College Medical School, Boston, 1928; member of the American Academy of General Practice; served during World War II; on the staffs of the Hamot Hospital, where he interned, and St. Vincent's Hospital; died May 29, aged 57, of coronary thrombosis.

LeComte, John Radway, Albuquerque, N. M.; Columbia University College of Physicians and Surgeons, New York City, 1903; veteran of World War I; died in the Veterans Administration Hospital May 15, aged 76, of heart disease.

Laing, Stanley Glen ✱ Kansas City, Kan.; St. Louis University School of Medicine, 1940; on the staffs of St. Margaret's Hospital, where he interned, and Providence and Bethany hospitals; died in Lakeview, Ark., May 26, aged 55, of acute coronary occlusion.

Lane, Louis Perpignan, Jr. ✱ Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, 1913; served during World War I; on the staffs of Coney Island, Victory Memorial, and Harbor hospitals; died May 30, aged 68, of arteriosclerotic heart disease.

Levi, Albert Abraham ✱ Minneapolis; Julius-Maximilians Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1908; member of the Illinois State Medical Society; died in Mount Sinai Hospital May 3, aged 72, of coronary thrombosis and hemiplegia.

Lhevine, Morris Boise, Tulsa, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1917; an associate member of the American Medical Association; member of the Radiological Society of North America and the American College of Radiology; specialist certified by the American Board of Radiology; for many years secretary of the board of directors of the Hillcrest Medical Center, where he was director of radiology and where he died May 19, aged 70, of arteriosclerotic heart disease.

Lofton, Frederick A. ✱ Chicago; Harvey Medical College, Chicago, 1901; served on the staff of St. Bernard's Hospital, where he died June 9, aged 82, of arteriosclerosis.

Lynch, William Joseph ✱ Weimar, Calif.; National University of Ireland, 1919; member of the American Trudeau Society; for many years on the staff of the Weimar Joint Sanatorium, where he died May 21, aged 58.

McCarthy, Patrick Henry, Cambridge, Mass. (licensed in Massachusetts in 1900); died in Arlington May 15, aged 82, of cerebral vascular accident.

McCarty, James Joseph, Jr., Chicago; Harvard Medical School, Boston, 1910; died May 28, aged 71.

McClellan, Ernest Edward ✱ Huntington, W. Va.; Medical College of Virginia, Richmond, 1933; on the staff of the Memorial Hospital; died July 4, aged 49, of a heart attack.

McCloskey, Edward William, Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1911; an associate member of the American Medical Association; fellow of the American College of Physicians; veteran of World War I; served on the staff of the Chestnut Hill Hospital; died in the Lankenau Hospital June 16, aged 71, of myasthenia gravis.

McDowell, Charles Albert ✱ Covina, Calif.; University of Pittsburgh School of Medicine, 1925; died May 14, aged 55.

McNamara, John Francis, Chicago; Loyola University School of Medicine, Chicago, 1921; served as senior surgeon at the Mercy Hospital; died May 29, aged 67, of bronchopneumonia.

Magill, H. Kelvin ✱ Lexington, Mass.; University of Colorado School of Medicine, Denver, 1937; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; served on the staffs of the Sancta Maria and Cambridge City hospitals in Cambridge, Boston City Hospital, Winchester (Mass.) Hospital, and the Brooks Hospital in Brookline; died in the Massachusetts General Hospital, Boston, May 14, aged 46, of coronary thrombosis.

Mahoney, Roy Bernard ✱ Chicopee Falls, Mass.; Georgetown University School of Medicine, Washington, D. C., 1925; veteran of World War I; school physician; physician for the Fisk division of the U. S. Rubber Company; on the surgical staff of the Mercy Hospital in Springfield; died May 26, aged 59, of diabetes mellitus.

Main, George Chrysup, Denver; St. Louis University School of Medicine, 1924; veteran of World War I; on the staffs of the St. Anthony and Presbyterian hospitals; died May 18, aged 58, of coronary occlusion and paralysis agitans.

Martin, Mary K., Los Angeles; Hering Medical College, Chicago, 1894; died in Verdugo City, Calif., April 16, aged 87, of virus pneumonia.

Mawhinney, Harvey Norton ✱ Pittsburgh; University of Pittsburgh School of Medicine, 1920; specialist certified by the American Board of Radiology; member of the Radiological Society of North America, fellow of the American College of Radiology; past-president of the Pennsylvania Radiological Society and the Pittsburgh Roentgen Society; on the staffs of the Sewickley (Pa.) Valley Hospital, Suburban General Hospital in Bellevue, and the Homestead (Pa.) Hospital, where he died June 17, aged 63, of injuries sustained in an automobile accident.

Meeks, John Alexander, Kite, Ga.; Hospital Medical College, Eclectic, Atlanta, 1911; died May 5, aged 73, of myocardial infarction.

Minshull, Harold Frederick, New Lexington, Ohio; Eclectic Medical College, Cincinnati, 1918; member of the Ohio State Medical Association; secretary of the Perry County Medical Society; county coroner; health commissioner of Perry and Morgan counties; on the staffs of the Bethesda and Good Samaritan hospitals in Zanesville; died May 21, aged 59, of coronary occlusion.

Mitchell, Edward Francis ✱ Clinton, Mass.; Harvard Medical School, Boston, 1922; served on the staff of the Clinton Hospital; died May 23, aged 70, of coronary thrombosis.

Mitchener, William Claude, Okmulgee, Okla.; Memphis (Tenn.) Hospital Medical College, 1902; an associate member of the American Medical Association; served as mayor; formerly on the board of the Okmulgee City Hospital; died in Oklahoma City May 24, aged 80, of myocardial degeneration, bronchopneumonia, and uremia.

Monteverde, Whitten Cantwell ✱ Brentwood, Calif.; St. Louis University School of Medicine, 1929; formerly practiced in Pittsburg, where he was a member of the city council; on the staff of the Pittsburg Community Hospital, died May 23, aged 53, of coronary thrombosis.

Moon, James P. ✱ Winchester, Tenn.; University of Nashville Medical Department, 1908; past-president of the Williamson County Medical Association; director of the Coffee and Franklin County Health Departments; served on the staff of the Mid-State Baptist Hospital, Nashville, where he died May 28, aged 74, of uremia.

Morden, Lucetta, Brooklyn, N. Y.; Trinity Medical College, Toronto, Canada, 1904; died in the Greenpoint Hospital June 2, aged 75, of heart disease, bronchopneumonia, and cancer of the gastrointestinal tract.

Munson, Henry Orson ✙ Rushville, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1890; on the staff of the Phelps Hospital in Macomb; died in Jacksonville July 14, aged 88, of coronary thrombosis.

Murphy, Edward John, Rochester, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1904; during World War II was associated with the U. S. Public Health Service, assigned to the Bureau of Printing and Engraving, Washington, D. C.; served on the staffs of the Rockaway Beach (N. Y.) Hospital, St. Joseph Hospital in Far Rockaway, and St. Mary's Hospital in Brooklyn; died in the Genesee Hospital May 24, aged 76, of carcinoma of the stomach.

Newsome, Levi J., Topeka, Kan.; Meharry Medical College, Nashville, Tenn., 1907; died in the Stormont-Vail Hospitals June 23, aged 82, of cirrhosis of the liver.

Newton, Herman Christian ✙ Chicago; Northwestern University Medical School, Chicago, 1905; also a graduate in dentistry; died in the Wesley Memorial Hospital July 1, aged 80, of a heart attack.

Nihart, Orrin H., Edon, Ohio; Starling Medical College, Columbus, 1898; served as coroner and as state legislator; affiliated with the Cameron Hospitals, Bryan; died in the Mound Park Hospital, St. Petersburg, Fla., May 29, aged 84, of ruptured aneurysm of the abdominal aorta and general arteriosclerosis.

Niven, Joseph Dougal, Tucker, Ark.; Vanderbilt University School of Medicine, Nashville, Tenn., 1894; University of Nashville (Tenn.) Medical Department, 1894; died in Little Rock May 17, aged 88, of carcinoma of the kidney.

Obers, Samuel Joseph ✙ New York City; New York University College of Medicine, New York City, 1937; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; served on the staffs of the Stony Lodge Sanitarium in Ossining, and the Beth Israel and Lenox Hill hospitals; died May 12, aged 42.

Peterson, Ralph Otto ✙ Racine, Wis.; Marquette University School of Medicine, Milwaukee, 1916; fellow of the American College of Surgeons; on the staff of St. Mary's Hospital; died June 6, aged 68, of cerebral hemorrhage.

Rowley, Antinous Gilbert, Middleton, Wis.; Rush Medical College, Chicago, 1899; served as health officer; died May 24, aged 81, of carcinoma of the prostate and essential hypertension.

Runkle, George Darius ✙ Stockton, Ill.; Northwestern University Medical School, Chicago, 1903; died July 3, aged 77, of abdominal carcinoma.

Sawyer, Dwight M. ✪ Glens Falls, N. Y.; Johns Hopkins University School of Medicine, Baltimore, 1911; past-president and secretary of the Warren County Medical Society; member of the Glens Falls Academy of Medicine; consulting physician for the Glens Falls Hospital, where he was past-president, vice-president, and secretary of the staff; an examining physician for the draft board during World Wars I and II; died May 7, aged 73, of aneurysm of the aorta.

Schrader, Merlin Arthur, Melbourne, Iowa; State University of Iowa College of Medicine, Iowa City, 1940; member of the American Society of Anesthesiologists; died in the Skiff Memorial Hospital, Newton, July 2, aged 42, of injuries received in an automobile accident.

Silliman, George Stephen ✙ Roanoke, Va.; Albany (N. Y.) Medical College, 1908; associated with the Veterans Administration; died in the Veterans Administration Hospital April 19, aged 73, of coronary thrombosis.

Smith, Alfred Nelson ✙ Glasgow, Mont.; Northwestern University Medical School, Chicago, 1911; on the staff of the Frances Mahon Deaconess Hospital; died in Havre June 22, aged 73, of peritonitis, following a ruptured diverticulum.

Smith, Nina Ream, Monterey Park, Calif.; Sioux City (Iowa) College of Medicine, 1900; an associate member of the American Medical Association; died in the Collis P. and Howard Huntington Memorial Hospital, Pasadena, June 2, aged 88, of coronary thrombosis.

Steinfeld, Julius ✙ Des Plaines, Ill.; Universität Heidelberg Medizinische Fakultät, Baden, Germany, 1920; member of the American Psychoanalytic Association and the American Psychiatric Association; medical director and owner of the Forest Sanitarium; died in Zurich, Switzerland, June 27, aged 60, of coronary occlusion.

Sturm, Ellis A., Atlanta, Ga.; Eclectic Medical Institute, Cincinnati, 1895; died April 30, aged 87, of arteriosclerosis and uremia.

Thewlis, Malford Wilcox ✙ Wakefield, R. I.; Medical School of Maine, Portland, 1911; founder and secretary of the American Geriatrics Society; author of "The Care of the Aged (Geriatrics)"; served as associate editor of *Medical Times;* on the staff of the South County Hospital, where he died June 3, aged 66.

Waugh, Fred Duvall, Riverside, Ill.; Northwestern University Medical School, Chicago, 1908; died in the Research and Educational Hospitals in Chicago March 4, aged 86.

Wells, George Marion ✙ Bowling Green, Ky.; Loyola University School of Medicine, Chicago, 1916; veteran of World Wars I and II; since 1931 director of the Warren County Health Department; from 1932 to 1936 medical advisor at the Western Kentucky State Teachers College; for many years practiced in Lafayette, Ind.; died recently, aged 68, of coronary thrombosis.

Whitledge, Herbert Edwin, Evansville, Ind.; University of Louisville (Ky.) Medical Department, 1897; veteran of World War I; served in the U. S. Public Health Service Reserve and the Veterans Bureau; at one time associated with the Veterans hospitals in Camp Kearney, Calif., and Outwood, Ky.; died in St. Mary's Hospital May 5, aged 81.

Williams, Arthur Grady ✙ Florala, Ala.; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1913; vice-president of the Bank of Florala; died May 16, aged 68, of coronary disease.

Wilson, Cas Pharaoh ✙ Sevierville, Tenn.; Lincoln Memorial University Medical Department, Knoxville, 1917; founder and medical director of the Wilson Hospital; died in the Fort Sanders Presbyterian Hospital, Knoxville, May 29, aged 64.

York, Marion Nicholas, Hawthorne, Calif.; University of Arkansas School of Medicine, Little Rock, 1920; died April 12, aged 63.

Young, Glyndon Angus, Minden, Nev.; State University of Iowa College of Homeopathic Medicine, Iowa City, 1900; formerly practiced in Ponca, Neb., where he served as mayor and county health officer; served overseas during World War I; died June 28, aged 80, of carcinoma of the prostate.

Young, Lawrence Randolph, Mandeville, La.; Kentucky School of Medicine, Louisville, 1906; died June 18, aged 73.

Zaborowski, Francis Leo ✙ Philadelphia; Temple University School of Medicine, Philadelphia, 1926; fellow of the American College of Surgeons; an instructor in surgery at his alma mater; on the staffs of the Northeastern and Temple University hospitals; died in Fort Washington, Pa., June 6, aged 35.

Zawislak, Joseph John ✙ Lawrence, Mass.; Middlesex College of Medicine and Surgery, Waltham, 1936; served overseas during World War II; formerly physician for the social disease clinic of the Municipal Health Department; school physician; on the staffs of the Lawrence (Mass.) General Hospital and the Bon Secours Hospital in Methuen; died May 10, aged 47, of coronary thrombosis.

Zenner, Philip ✙ Cincinnati; Miami Medical College, Cincinnati, 1875; professor emeritus of neurology at the University of Cincinnati College of Medicine; member of the American Neurological Association; oldest retired staff member of the Jewish Hospital; died June 25, aged 104.

FOREIGN LETTERS

AUSTRIA

Meeting of Gynecologists.—The fourth Congress of Austrian Gynecologists met in Bad Ischl in June.

Uterine Prolapse.—Dr. T. Antoine of Vienna stated that in uterine prolapse operation should be performed, provided there are no general contraindications. Treatment with a pessary may be considered only in exceptional cases. The operative methods vary greatly and the choice depends on the preference of the operator, the degree of the prolapse, the patient's marital status, and the presence or absence of urinary incontinence. The simplest operation is colporrhaphy, by which satisfactory results are obtained in patients with moderate prolapse, when the operation is combined with restoration of the position of the bladder and the construction of a high perineum. Interposition is still an effective method in women of advanced age with large cystoceles. Its use is now greatly reduced by the Manchester operation, which also yields excellent results. Lifting up or fixation of the cervix may be obtained also by other operations such as Kjelland's or by shortening or fixation of the sacro-uterine ligaments at the cervix. Hysterectomy should be performed only exceptionally in patients with a normal uterus. Halban's operation, which consists of amputation of the cervix and obliteration of the vesico-uterine excavation with subsequent colporrhaphy, proved to be valuable in patients with lesser degrees of prolapse. In women of advanced age, one may perform a vaginal obliteration, with or without obliteration of the vulva, or simple obliteration of the vulva. The Spalding-Richardson operation consists of amputation of the body of the uterus and of the cervix, and in this operation only the supravaginal portion of the cervix is spared. It is supposed to provide better support to the vagina by preserving the cardinal ligaments. Other recent techniques include the cutaneous transplantation (Ruiz-Arce), the interposition-like technique (Thiessen), the insertion of tongues of cartilage into the interior vaginal wall (Gallo), and the sagittal gathering up of the vagina (Lorbeer). Only in rare cases is it necessary to perform a laparotomy in the course of operation for prolapse.

Vaginal Operation for Prolapse.—O. Käser of St. Gallen reported a series of 872 vaginal operations for prolapse and 3 exohysteropexies. Ten patients with prolapse and severe general disease were treated with the aid of a pessary. Twenty per cent of the women operated on were over 60 years of age, the oldest being 90. In 63% an anterior and posterior plastic operation was performed, and in most of these the cervix was amputated and the cardinal ligaments were gathered up. In 37% the uterus was extirpated by the vaginal route, either because of climacteric hemorrhages or fibromyoma or because of extensive or total prolapse in patients of advanced age. In nearly 33% various additional operations were performed. No operative deaths (for up to 30 postoperative days) occurred. The most important postoperative complications were pyuria (20%), a febrile course (12%), thromboses (2.5%), and embolism (1.3%). The number of thromboembolisms was markedly reduced by systematic physical and chemical prophylaxis, but the incidence of hemorrhages (4.4%) was increased. Follow-up observations of 64% of the patients were made, and recurrences were observed in 12 patients (in 3 of them after additional deliveries). Incontinence of urine had been present in more than 50% of the patients; in 90% of these a complete recovery resulted from the operation, 7.5% were improved, and 1.8% were therapeutic failures.

Uterine Prolapse in Women of Advanced Age.—S. Kolonja of Klagenfurt reported on an operative technique that consists of anterior colporrhaphy, extensive colpoperineal repair, and obliteration of the vulva with construction of a high muscular perineum that extends to the opening of the urethra. A fourfold supportive effect is thus obtained. The last act of the obliterating operation, the establishment of a muscular plate that is able to provide support and which is obtained with the aid of the levator ani, the bulbocavernous muscles, and deep and superficial perineal muscles, is essential for a lasting good result. Ninety-eight women were operated on by this method, and, of these, 80 had had total prolapse and 18 partial prolapse. The age of the patients ranged from 55 to 83 years. All the patients obtained a satisfactory plastic result and were free of symptoms when they were discharged. There were no postoperative deaths. There were no recurrences in the 91 patients who could be followed up. Because the anatomic and functional results were highly satisfactory in all patients, the speaker felt justified in recommending this technique.

Pain-Relieving Operations.—Dr. Krüger of Bad Ischl stated that operations for relief of pain should primarily be limited to thoracic or, even better, perhaps, to cervical chordotomy. The pain with which the gynecologist has to deal is primarily caused by irritation of the lumbosacral plexus and the cervical plexus. Complete relief of pain may be obtained with chordotomy in the form of sectioning the spinothalamic tract. With correct technique, impairment of the pyramidal tracts and of the anterior spinal artery can be prevented. The results with high cervical chordotomy are generally excellent. A presumptive survival time of about three months must be required for considering this operation as indicated. The speaker advises against prefrontal leukotomy for relief of pain, because of the great psychic changes associated with its use and because the patients with pain are not as a rule mental patients. In patients who are expected to die within a few months, morphine is still the drug of choice.

Puerperal Mastitis.—P. Elsner and W. Thewanger, of Vienna, believe that the increased incidence of mastitis is related to the increasing and often ill-advised use of chemotherapeutic agents and particularly of antibiotics. Certain criteria, such as comparison of the total duration of the preoperative and that of the postoperative course and the rate of recurrences, suggest that treatment by conservative means (application of heat and withdrawal of milk by a breast pump) is to be preferred to the additional use of chemotherapeutic agents. These observations are supported by determinations of bacterial resistance and culture studies. In 93% of the patients Micrococcus pyogenes var. aureus was found to be the pathogen, and in 84% it was resistant to penicillin.

Metrorrhagia.—H. Zacherl of Vienna said the observation that the first hemorrhage associated with placenta previa is almost never fatal and that the same applies to subsequent hemorrhages, provided the hemoglobin level is normal, seems to suggest expectant treatment for patients in whom pregnancy has not yet progressed to full term. This procedure, however, depends on the existence of a well-organized blood bank and complete preparedness for surgical treatment. Thus, the high mortality rate among immature infants when the mother has placenta previa can be greatly reduced without endangering the life of the mother. Acquired hemorrhagic diathesis may be associated with certain complications such as ablatio placentae, severe toxicosis, missed labor, extensive Rh immunization, and amniotic fluid embolism. Such hemorrhages, which may be uncontrollable, depend on a fibrinogen deficiency, which is a rare occurrence. The mechanism of their production warrants the conclusion that a too active obstetric management may favor such hemorrhagic diathesis, and it should therefore be avoided.

Retention of the Placenta.—E. Leinzinger of Graz stated that, by filling the placenta through the umbilical vein with 70% iodopyracet injection, it has been possible for the first time to elucidate roentgenologically the causes of the placental retention in situ. In addition to abnormal structure and abnormal insertion of the placenta, mechanical impediments may also be responsible for

The items in these letters are contributed by regular correspondents in the various foreign countries.

the retention of the partially detached placenta or for the incarceration of the detached placenta. Retention of the placenta is rare if methylergonovine tartrate is used as soon as the indications are clear. In one patient expression of the placenta was not performed at the optimal time, and incarceration of the placenta, recognizable in the roentgenogram, resulted.

Diabetes and Pregnancy.—G. Mestwerdt of Halle stated that the fertility of diabetic women can now be greatly increased (from 2 to 28%) and the mortality of mothers and infants could be decreased from 50 to about 1%. Early diagnosis and differentiation of pancreatic diabetes and hypophyseal diabetes are essential. It is difficult to influence the course of the latter form, which is responsible for infant death rates up to 50%. Since glycosuria is observed frequently in pregnant women, the diagnosis may be established only by an increased blood sugar level. Latent diabetes may frequently become manifest for the first time in pregnancy. A history of preceding stillbirth, malformations, and gigantic infants presents certain indications. Toxicosis is a frequent complication (30% more frequent when associated with diabetes). The incidence of malformed infants is about 10%. Pregnancy makes every patient with diabetes worse by disturbing the hypophyseal regulatory mechanism. While some stabilization may occur in the middle of the gestational period, the onset and the end of pregnancy are associated with great lability of the blood sugar level. Metabolic relationships between mother and fetus increase this lability. There is a changed responsiveness to insulin that frequently results in hyperglycemia. The hyperglycemic blood of the mother stimulates formation of insulin in the fetus. This does not pass the placenta but exerts an increased absorption effect on the sugar by a reduction of the fetal sugar in the blood. With too large a dose of insulin, hypoglycemia results in mother and infant, and the fetus may die. Strict and constant control is, therefore, essential. In the infants, control of the blood sugar level is of less importance, since it is highly labile even under normal conditions. Administration of glucose by mouth is indicated. Increase in weight occurs slowly in most patients because of the slow reduction of the edema. Birth trauma occurs frequently, and, therefore, cesarean section seems to be the best form of delivery, preferably in the 36th week of pregnancy. Extremely early section was abandoned because of increased mortality of the infants. The indications for cesarean section in these patients are: toxicosis, characteristic complications such as gigantic fetus, signs of fetal maturation despite short gestation (roentgenographic measurements of the fetal length), threatened psychoses of the mother at the end of pregnancy with risk of shock and coma, advanced age of primiparas, and history of several stillbirths.

Radioactive Isotopes.—E. Schwach of Vienna injected radioactive gold (Au^{198}) directly into the tumors of patients with still limited recurrences in the pelvic wall after hysterectomy for carcinoma of the uterus. In patients in whom intratumoral application was impossible, a strip saturated with the remaining portion of the isotope was placed on the carcinomatous focus, which had been made accessible by laparotomy. Temporary fixation was performed in order to obtain an optimum local irradiation effect. From 120 to 200 curies was applied per treatment. Despite the large dose, neither a carcinolytic irradiation effect in the recurrent tumor nor a growth-inhibiting effect on the carcinomatous spread was observed. The Au^{198} is distributed too rapidly within the body, and thus a low-dose local irradiation effect may be obtained, which causes temporary relief of pain in most cases. Appreciable rests of the isotope could still be demonstrated with the Geiger counter in the patient's body after two months, and they were stored in higher concentration in the spleen than in the injected pelvic organs. Because of these observations, the speaker refrained from further therapeutic application of Au^{198} in treating recurrent pelvic tumors.

Embryopathy Without Manifest Disease of the Mother.—E. Engelhart of Graz said embryopathies may be classified as viral, deficiency, toxic, and those caused by irradiation. An atypical form has also been observed. In contrast to the typical viral embryopathy, this was a viral embryopathy with no sign of infectious disease of the mother during early pregnancy. The patients had had the viral disease in their childhood and had acquired immunity. The malformations in their infants were caused by a viral disease of a child who lived in close contact with the pregnant woman during her early pregnancy. The woman during her early pregnancy acts as a carrier of the virus and transmits it to the embryo. The first case was that of a malformation and premature birth resulting from the mother's exposure, early in pregnancy, to German measles in an older child. There was no simultaneous disease in the mother, who had acquired immunity at the age of 3 years. The second case was one of intra-uterine fetal death and abortion after several children had had whooping cough without simultaneous disease of the mother during the early pregnancy. This mother had had whooping cough when she was 3 years old and was reexposed to the infection in the 20th week of her pregnancy. Miscarriage of the infant, who had died in utero, occurred after 25 weeks. In the third case the mother was in her fifth week of pregnancy when her first-born child got scarlet fever. She attended this child during the entire infectious period, and the fetus developed a severe cardiac malformation. It was concluded that this type of viral embryopathy will be the cause of malformations more frequently than that caused by German measles, because most women have acquired immunity to this disease in childhood. Furthermore, some of the unknown causes of congenital malformation, which cause to about 42% of the total, can be explained in this way. Protection can be obtained only by effective prophylactic treatment, which consists of separation of the mother in early pregnancy from her children with virus disease.

Thrombopenia During Treatment with Reserpine.—At the meeting of the Society of Physicians of Vienna on June 29, Dr. K. Schmidt reported the case of a 56-year-old patient in whom a hemorrhagic diathesis with thrombopenia developed during treatment with reserpine. There was an increase in thrombocytes and a disappearance of hemorrhagic diathesis after corticotropin was given in place of reserpine. The decrease in thrombocytes was by crisis, and hemorrhagic diathesis recurred after a small test dose of reserpine was given, symptoms being demonstrable after six hours. There was no retraction of the blood clot when reserpine was added in vitro to the patient's blood, and the retraction of the clot was poor without the addition of the drug. These manifestations disappeared after treatment with corticotropin, but the thrombocytes again decreased when treatment with corticotropin was discontinued, even though no more reserpine was given.

Eczema Herpetiforme.—At the same meeting, Drs. W. Lindemayr and C. Eberhartinger reported a series of nine patients with eczema herpetiforme. This disease is produced by the infection of the eczematous skin with the virus of herpes simplex and must be distinguished from similar lesions, particularly from eczema vaccinatum. The virus of herpes simplex could be demonstrated in all of the seven patients so tested. Three patients showed involvement of the cornea or the eyelids. The course was benign in all of the patients. To what extent this was the result of the use of the chlortetracycline given cannot be said because the condition tends to heal spontaneously.

Sudden Pressure Changes.—At the same meeting, H. Kolder reported experiments on explosive decompression carried out on rats in a glass the shape of a truncated cone. The immediate results of explosive decompression were investigated with pressures of 0.1 kg. per square centimeter and a pressure difference from 0.4 to 0.9 kg. per square centimeter with pressure equalization times of 1.3 to 15 milliseconds. Immediately after the decompression, respiration ceases and the electrocardiogram shows a decrease in frequency. Animals that had been subjected to vagotomy continued to breathe after the decompression, but after from 15 to 20 seconds even the vagotomized animals showed bradycardia together with electrocardiographic signs of a cardiac disorder induced by hypoxia. The instantaneous arrest of respiration and the bradycardia are caused by stimulation of the vagus nerve, which in turn is produced by the expansion of air in the dilated lung as the result of the decompression. The changes observed in the electrocardiogram after from 15 to 20 seconds, even in the vagotomized animals, are caused by arterial air embolism. Air bubbles can be demonstrated in the heart.

Artificial pneumothorax protects against the results of explosive decompression, that is, the arterial air embolism cannot have been caused by the liberation of gases in the blood. With

the aid of high-speed photography, it was possible to follow the course of the expansion of the thorax after decompression. There was a noticeable outflow of air from the mouth after 3 milliseconds, and after 5 milliseconds the expansion of the thorax begins. This expansion is maximal at the end of 20 milliseconds, and, after from 60 to 70 milliseconds, the thorax again commences its contraction. The results of decompression depend on the outflow of the air that has expanded.in accordance with the pressure decrease in the lung, and on the concurrent expansion of the thorax as a result of the decrease in pressure around the body. Exact values can be given for the pressure difference and decompression time that are just bearable. In the presence of a pressure difference of 0.9 kg. per square centimeter, for instance, the decompression time must be longer than 40 milliseconds in order to avoid the afore-mentioned results. Functional manifestations and autopsy findings indicate that the same process takes place during explosive decompression and in injuries produced by air blast.

Evaluation of Clinical Findings.—At the same meeting, E. Bukovics and F. X. Wohlzogen said that statistical analysis is difficult or impossible when clinical findings are not expressed in definite figures. This is particularly the case in the evaluation of a patient who is being treated with a new drug, the efficacy of which is unknown. In such cases there are only three criteria that can be applied to the evaluation: improved, unchanged, or made worse. The question arises whether it is possible to deduce the therapeutic efficacy from the number of improved patients in a group of patients who have received the same treatment. This problem was solved as follows. In accordance with the clinical findings, each patient was given a numerical factor; thus, +1 stood for improved, 0 for unimproved, −1 for made worse. These figures were added. A spot check of the factor n (number of patients) thus receives a certain value z (sum of evaluations). Assuming that, without the administration of the therapeutic substances to be tested, an equal number of patients would be improved, unimproved, or made worse ($z=0$), it is possible to compute exactly the probability of every fortuitous deviation of the value of z from 0.

ITALY

Infant Death Rate.—Recent statistical reports indicate that the deaths in the first year of life in Italy have decreased from 58.4 to 52.8 per 1,000. This is attributed to improved medical care, the use of new drugs, and improved living conditions. The number of accidental deaths due to such things as falls, drownings, and road accidents exceeds that due to disease.

Hereditary Tumors.—At the meeting of the Medical Academy of Pistoia in April, Professor Cianferrari stated that hereditary predisposition to formation of tumors exists in some persons. This is especially true in tumors of the stomach and breast. Those of the uterine cervix and of the bladder appear not to be hereditary, and tumors of the uterine fundus and of the prostate may or may not be inherited. The speaker emphasized the fact that, even though tumors may be considered biologically hereditary, the probability that such a tumor will develop in any given person is not much greater than the probability of formation of tumors in the general public.

PERU

Treponematosis.—Further evidence that treponematosis originated in the Americas is presented by Prof. Pedro Weiss (*Ginecologia y Obstetricia*, volume 2, number 1, 1956), who found in pre-Colombian cemeteries adults' bones with lesions identical to those now known to be caused by syphilis. There is further evidence that, of the three treponematoses (syphilis, yaws, and pinta), pinta arose first. Syphilis is an urban disease and does not need an insect vector, while yaws and pinta are rural diseases and are transmitted by insects. Since yaws and pinta have epidemiological features that render them likely to arise under the conditions found in the tropical jungle, they may be as old as the jungle, whereas syphilis requires concentrations of population such as were not found until agricultural cultures were formed many thousands of years later.

President-Elect of Peruvian Federation.—Dr. Froilán Villamón, president-elect of the Peruvian Medical Federation, in an address before the federation said that one of the most important problems in medical education is the creation of a code of medical ethics. There is also a great need to place medical research on a firmer scientific basis. Dr. Villamón pledged himself to fight for free choice of physician and clinic by beneficiaries of the social insurance agency.

The Menopause.—In *Ginecologia y Obstetricia* (volume 2, number 1, 1956), Dr. Normando Arenas and co-workers state that, in a series of 1,000 women in the menopause, the average age at menarche was 13 years 9 months and the average age at menopause was 48 years 8 months, giving an average of 34 years 11 months of potential child bearing. The fact that this figure is slightly less in women of European origin is explained by environmental rather than racial factors.

UNITED KINGDOM

BCG Vaccine.—Since 1949, when BCG vaccine began to be used on a large scale in the United Kingdom, the standard liquid BCG vaccine manufactured by the State Serum Institute of Copenhagen has been used. Although this vaccine has given a conversion rate of practically 100% within six to eight weeks, it has become clear that liquid BCG suspensions have certain disadvantages. These include the necessity for using them fairly soon after preparation, a tendency to the production of unsightly scars, and the inability to test them for their content of viable organisms because of the fact that the vaccine is released for use soon after preparation. A freeze-dried vaccine is now available in the United Kingdom, and Lorber and co-workers (*Tubercle* 37:187, 1956) have investigated its use in 276 newborn infants in Sheffield. They report that six weeks after vaccination the reaction to tuberculin was positive in only 80% of the vaccinated infants, but 12 weeks after vaccination it was positive in 94%. The local lesions produced by the freeze-dried vaccine were much smaller than those produced by the Danish vaccine and were neither painful nor disfiguring. They usually disappeared by 12 weeks after vaccination. Enlargement of the axillary lymph nodes was infrequent, and the nodes never discharged or suppurated. On the other hand, in 11 of the 106 infants vaccinated with the liquid vaccine, a large papule with a large central ulcer developed; axillary lymph-node enlargement was common; and the large lesions took many months to heal. The freeze-dried vaccines were kept at room temperature for 19 to 28 weeks without apparent loss of antigenicity.

Incidence of Circumcision, Tonsillectomy, and Appendectomy in Recruits.—The incidence of circumcision, tonsillectomy, and appendectomy among 1,434 Royal Air Force recruits, aged 17 to 24 years, was investigated by Stuart Carne (*Brit. M. J.* 2:19, 1956). Circumcision had been performed in 34.4% (less than 1.5% of the recruits were Jewish). The incidence was higher in those from "public" schools (41.9%) than in those from "elementary" schools (32.8%). The most striking difference, however, was the much lower incidence (25.5%) among the 137 recruits who came from Scotland. Tonsillectomy had been performed in 31.9% of the recruits, and nearly 67% of the operations had been performed when the subject was in the 4-to-8-year age group. There were no national differences, but the incidence was significantly higher among recruits from grammar and public schools (37%) than among those from elementary schools (28.9%). Appendectomy had been performed in 8.4% of the recruits.

Annual B. M. A. Meeting.—The annual representative meeting of the British Medical Association, held in Brighton, was enlivened by an introductory debate as to whether members should

be allowed to smoke while the meeting was in session. Convinced that not only lung cancer but also coronary thrombosis and bronchitis are undoubtedly brought on by smoking, the meeting agreed that smoking should not be allowed during the meetings. A statement in its annual report that the council believes the National Health Service likely from time to time to be the subject of political controversy led to much discussion. One member said that if the health service were divorced from politics it need not annually cost 1.12 billion dollars. In his opinion the council could have called a conference of the political parties, approached the Prime Minister and the leader of the opposition, and informed the public that the profession was tired of being the football of the two political parties. A member of the council admitted that it was a bad thing that medicine should be to some extent bedeviled by politics, but so far the council had been unable to find any practical solution to the problem.

In a motion expressing alarm at the continued influx of immigrants found to be suffering from communicable diseases and recommending that appropriate action be taken, a member said that persons with tuberculosis were entering the country in far greater numbers than the Ministry of Health was willing to admit. At one clinic in London, of 78 beds provided for the treatment of pulmonary tuberculosis, 26 were permanently occupied by Irish immigrants. There appeared to be no effective statutory power to prevent the entry into the country of persons suffering from active pulmonary tuberculosis. Britain was almost alone in the Commonwealth in not requiring an examination and certificate of fitness from prospective immigrants before leaving the country of origin. Another member of the council said that all that stood between this resolution and its implementation was the ever-open-door policy to immigrants from practically all over the world to Britain.

The Oxford division moved that access to the National Health Service should not be available to foreign tourists in Britain except in the case of nationals of countries with which there are reciprocal arrangements. This motion did not apply to foreigners who were resident for a long period or who were studying in Britain. Another member stated that about 18 months ago six American women were taken into Southampton Hospital with fractured femurs due to a rough crossing of the Atlantic. Although one of them was fit enough to go home after an eight-weeks' stay in the hospital, she said she could not afford the treatment in the United States and remained in the hospital six more weeks. Other members took pride in being allowed to offer hospitality to those who come to Britain for any purpose. The motion was rejected by a vote of 153 to 135.

The meeting carried a motion expressing chagrin at the refusal of the Home Secretary to legalize the administration of morphine by competent nurses in serious industrial accidents. It was reported that some time ago a deputation from the Royal College of Nursing and the British Medical Association went to see the Home Secretary to request an amendment to provide that competent nurses employed in industry should be allowed to administer morphine in cases in which there was likely to be delay in getting a physician to the scene. The Home Secretary refused to agree to this, pointing out that the proper way to provide for a serious accident was to ensure that there were arrangements for securing the early attendance of a physician. In opposing the motion, a member from the Durham coalfield said that he did not consider it fair to put this extra responsibility on nurses. A patient in shock requires intravenous administration of morphine in many cases, and that is not a procedure for a nurse to carry out.

The Burst Abdomen.—At the annual meeting of the B. M. A., Mr. Harold Park reported that, in 10,166 laparotomies performed at three general hospitals in Brighton over a five-year period, wound dehiscence occurred in 140, or 1.3%. When appendectomies were excluded, the figure was 2.1%. Most bursts occurred about the fifth or sixth day, and upper abdominal incisions were more prone to rupture than those of the lower abdomen. The case fatality rate was about 30%. He distinguished two types. One occurred in debilitated patients, in whom the wound never showed any signs of healing. The other, and more important, type occurred in patients in good condition and was preceded by a serosanguineous discharge from the wound. This type occurred usually in patients in the fifth, sixth, and seventh decades, and more than a third were in patients with malignant disease. Catgut had been used in 72% of the bursts. A precipitating factor was always increased abdominal pressure, usually due to coughing, vomiting, or ileus. Mr. Selwyn Taylor, in discussing this second type, made a plea for a study of the bacterial flora of the serosanguineous discharge, which could appear as early as 24 hours after operation. It did not appear to matter what type of suture material was used. In experimental wounds the introduction of antibiotics had improved the tensile strength of sutures, which suggested that asepsis was important. The speaker could find no record of a burst following a transverse abdominal wound.

Cost of Health Service.—The Minister of Health stated that the cost of the health service per capita of civilian population in England and Wales, exclusive of that met by payments by persons using the services, was estimated for 1956-1957 to be nearly $34 for all services provided as part of the health service. The estimated total cost to the health service in the current fiscal year resulting from increases in the prices of food and other hospital purchases is about $10,920,000. The cost to the Ministry of Health of a full years' supply of welfare milk to an individual child was $23.37; but this increased to $25.53 on July 1, when the price of liquid milk was increased.

New Poliomyelitis-like Disease.—After reviewing several mysterious outbreaks of an illness akin to poliomyelitis, the *Lancet* of May 26 concludes that a new disease involving the central nervous system has made its appearance. It is characterized by symptoms and signs of damage to the brain and spinal cord, protracted muscle pain, and emotional disturbances in convalescence, but it has a relatively benign outcome. One outbreak occurred in northwest London last summer, the second involved young British soldiers stationed in Berlin, and a third occurred in Iceland.

National Versus White Flour.—The independent panel appointed by the government to study the nutritive values of flour supported the industry against the government's medical and scientific advisers. Millers and bakers had claimed that nutritional differences in composition between national flour of 80% extraction (produced when 100 parts by weight of uncleaned wheat have been milled to give 80 parts by weight of flour) and the prewar flour of 70 to 72% extraction, when the latter was enriched with vitamins and iron, were insignificant. The government's medical and scientific advisers and the Medical Research Council claimed that, if the extraction rate were lowered to 70%, and even if thiamine, nicotinic acid, and iron were restored by enrichment, a reduced intake of other vitamins might in some circumstances cause nutritional deficiences. Flour of 80% extraction is, however, unpopular with millers, because it tends to be grey. The panel was impressed by the evidence for the demand for white flour and white bread. The professional pride of the miller in producing as clean and white a flour as possible is one reason for this preference. The bakers prefer a low extraction flour because it is easier to handle and from it they can produce more appetizing bread, rolls, cakes, and biscuits. Even the public prefers bread and cake made with the whiter grades of flour. The scientific arguments by the experts and advisers were not disproved but merely gave way to a popular demand.

Twins Born Twelve Days Apart.—Twins have been born 12 days apart at the Bearsted Jewish Memorial Hospital, Stoke Newington. The mother went into the hospital on May 17, and the first of the twins, both boys, was born on May 18. The second arrived on May 30. Mother and twins are well. This is the longest gap between twin births in the history of the hospital.

LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Malpractice: Release of Tortfeasor as Precluding Malpractice Action Against Doctor for Alleged Aggravation of Injury.—The plaintiff filed suit for damages alleged to have been caused by the defendant physician in his treatment of injuries received by the plaintiff in a certain automobile collision. From a judgment in favor of the defendant, the plaintiff appealed to the court of civil appeals of Texas.

In April, 1953, the plaintiff was injured by an automobile being driven by one Harrison and the following November he filed a suit for damages against Harrison. On April 23, 1955, the plaintiff instituted the present suit against the defendant physician, who had treated him for the injuries received in the automobile accident, alleging that the treatment was negligent in many particulars and caused him to suffer a greater disability than he normally would have from the original injury. Nine days later he executed a release to Harrison, releasing Harrison, his agents, assigns, etc., from any and all claims, actions, and causes of action, which he had then or might thereafter have or assert as a result of personal injuries received in the accident. The suit against Harrison was then dismissed. Following such dismissal, the present defendant filed a motion for summary judgment based upon the proposition that the release signed by the plaintiff to Harrison as a matter of law released his cause of action against the defendant. The evidence showed that the plaintiff had not intended to release the defendant when he executed the release to Harrison and that neither he nor his attorney realized that such release would have the legal effect of releasing his entire cause of action and preclude him from a recovery against the physician who allegedly, through negligence, aggravated such injuries.

The facts in the case, said the court, are without dispute, and there is nothing in the pleadings or evidence of the plaintiff tending to establish that the defendant's treatment caused a new injury; the pleadings as well as the plaintiff's own testimony are both to the effect that the defendant's treatment contributed to the old injuries and effected an aggravation of such injuries. The dominant question posed by this appeal is whether a release by an injured party of the one responsible for his original injury bars an action by the injured party against a physician or surgeon for negligent treatment of the injury.

In a prior Texas case, based upon an almost identical factual situation, it was held that where a plaintiff was injured in a motor bus accident and settled the claim against the bus company and released it from any and all liability of every kind and character, whether known or unknown, growing out of or incident to the accident, such releases operated to discharge the attending physician from liability to the plaintiff for allegedly negligent treatment of such injuries. By the weight of authority, continued the court, a general release by the one responsible for the releasor's original injury bars action by the injured party against a physician or surgeon for negligent treatment of the injury. We believe, the court concluded, that the Texas rule and the general rule, which is followed in some 44 states, represents the sound position. It is not difficult to find justification for the prevailing view when we consider that the injured party has the legal right to recover from the original wrongdoer all his injuries and damages, including subsequent maltreatment and subsequent injuries. If there is liability, let it fall on the wrongdoer who originated the injuries, and not on the medical practitioner who is serving mankind in a none too appreciative world. When the injured party elects to release the one who is primarily liable for his injuries, it is neither unjust nor inequitable to hold that his release of the wrongdoer serves to release also the physician who treated him at a time when he needed treatment and relief from suffering.

Accordingly, the judgment of the trial court in favor of the defendant physician was affirmed. *Borden v. Sneed, 291 S.W. (2d) 485 (Texas, 1956).*

Malpractice: Unauthorized Removal of Uvula During Tonsillectomy.—This was a malpractice action against the defendant surgeon for having removed a child's uvula during an operation for the removal of her tonsils and adenoids. From the action of the trial court directing a verdict for the defendant on all three counts of the plaintiffs' complaint, the plaintiff appealed to the Supreme Judicial Court of Massachusetts.

There were three counts in the plaintiff's complaint. The first two charged the defendant with the negligent removal of the uvula. The Supreme Judicial Court held that the trial court was correct in directing a verdict for the defendant on these two counts because there was no evidence of any unintentional removal of, or injury to, the uvula. The defendant testified that he intentionally removed the uvula after telling the plaintiff's parents that he would do so and why. There was no evidence that in performing the operation he did not conform to the standard of care required of physicians in the circumstances.

The third count, however, was for the unauthorized removal of the uvula. The plaintiff's father testified that the defendant advised removal of the plaintiff's adenoids and tonsils. He denied that he authorized the defendant to remove or touch any other part of his daughter's mouth. The plaintiff's mother testified that a month before the operation the defendant suggested the removal of the plaintiff's tonsils but did not mention adenoids or uvula.

The defendant, on the other hand, testified that he was a general practitioner who did a great deal of surgery; that he had intentionally removed an uvula two or three times, the last time about 10 years before because of a suspicious lesion; that here there was a background of cancer of the throat in the plaintiff's brother, which had "initiated . . . apparently, in the uvula, and ending in death . . . we do know that some families . . . have more of a tendency . . . to cancer than others . . . with that history . . . [and] especially where we have an elongated uvula that's causing a continuous hacking cough, where the youngster can't eat well and can't sleep well and is losing weight and has a secondary anemia with it—under those cases, that uvula should be and was removed" and that he removed it "after he had explained to the child's parents very carefully that the uvula is an elongated substance, a vestigial structure . . . with absolutely no function . . . [and that] it should be removed" there being the stated history of cancer. The defendant testified also that at that time he had read to the plaintiff's mother an article by a throat specialist that proved that the uvula is a remnant tissue with no function and a background for germs.

The father also testified that a week after the operation he asked the defendant "what had happened to the child's palate, that 'it was not there' " and that the defendant replied that the father "referred to the uvula, that he had not touched the uvula, that it had shrunk and that it would come back to normal in a few days."

On the testimony taken most favorably for the plaintiff, said the Supreme Judicial Court, the defendant had authority to do whatever was implied in the consent to remove adenoids and tonsils. It could not be ruled, however, that consent to the removal of the uvula was necessarily implicit in the authority given. There was no medical testimony that it was usual to do this. There was no suggestion that the defendant found anything when operating that made it reasonable then forthwith to remove the uvula as a part of what was being done. On the contrary the defendant stood expressly on what he saw and learned prior to the operation. The little relevant testimony shows the defendant dealing with this as an operative act that was additional to the removal of tonsils and adenoids in usual course and was carefully explained as such to the assenting parents. We think, concluded the court, that it was a jury question whether the defendant had authority to remove the uvula and that the verdict was wrongly directed under count three. Even if there was a lack of evidence, as the defendant contended, of connection between the plaintiff's postoperative troubles and loss of the uvula, the plaintiff was entitled to at least nominal damages for such an unauthorized act.

The plaintiff's exceptions to the ruling of the trial court in relation to the first two counts were therefore overruled, but the exception relating to the third count was sustained and the finding for the physician reversed. *Reddington v. Clayman, 134 N. E. (2) 920 (Mass., 1956).*

Chiropody as Practice of Medicine and Surgery.—This is a declaratory judgment proceeding in which the plaintiff, Medical Care, Inc., seeks determination of the question whether it is required to pay, under its contracts, charges incurred by subscribers for treatments that they have received from certain practioners of chiropody. The trial court held that the plaintiff is obligated under its contracts with subscribers to pay for services rendered by chiropodists, provided such services consist of medical, mechanical, or surgical treatment of ailments of the human hand and foot with the use of local anesthetics. From this order the plaintiff appealed to the Supreme Court of Appeals of West Virginia.

The questions presented by the certificate of the circuit court, said the Supreme Court of Appeals, are (1) whether a chiropodist is a duly licensed physician within the meaning of the state's enabling act for medical care plans, and is eligible to participate in the medical service plan operated by the plaintiff, and (2) whether the plan operated by the plaintiff embraces within its scope or contracts treatment by a chiropodist and entitles him to payment by the plaintiff for such treatment according to its contracts with its subscribers and the schedule of payments provided in such contracts.

Under the contracts between the plaintiff and its subscribers, in consideration of certain dues paid by them, said the court, the plaintiff agrees to pay for certain medical and surgical treatment on the basis of a schedule of fees specified in the contracts for various medical and surgical services. A physician can become a participant in the plan by agreeing to comply with the specified schedule of fees. If the medical services are furnished to subscribers by a physician who does not participate, the plaintiff agrees to pay 75% of the fee specified in the schedule. The contracts do not expressly cover services furnished by chiropodists, and services by them were not taken into consideration when the rate of the dues required to be paid by subscribers was fixed by the plaintiff and approved by the insurance commissioner. The plaintiff asserts that if its plan should be extended to cover treatment by chiropodists it will be necessary to revise the rate of the dues in order to preserve the financial solvency of the plan as presently operated by it.

A consideration of the applicable statutes, said the court, indicates clearly that a duly licensed physician or surgeon is authorized to treat any human ailment or infirmity by any method and that a duly licensed chiropodist, though authorized to treat medically, mechanically, and surgically without the use of anesthetics other than local, the ailments of the hand or foot, except the amputation of the foot, hand, toes, or fingers, and to fit and recommend appliances for correction or relief of minor foot ailments, is limited to those areas and those ailments in the practice of medicine and surgery. A duly licensed physician and surgeon is authorized to engage in the practice of chiropody, but a duly licensed chiropodist may not practice medicine and surgery except within the limits expressly imposed by the statute.

The statutes relating to the licensing of chiropodists exclude chiropodists from the category of duly licensed physicians and surgeons by forbidding chiropodists to use the title "doctor" except in connection with the word "chiropody or chiropodist." The statute broadly defining the practice of medicine and surgery as the treatment of any human ailment or infirmity by any method, expressly states that its provisions shall not apply to regularly licensed or registered chiropodists.

It is clear, concluded the Supreme Court of Appeals, that a duly licensed chiropodist is not a duly licensed physician within the meaning of the West Virginia statutes and is not eligible to participate in the plan of a medical service corporation for medical and surgical care furnished by duly licensed physicians to its subscribers under the terms of their contracts with such corporation. A medical service corporation is authorized to contract with the public and duly licensed physicians only for such medical and surgical care as may be furnished by duly licensed physicians and for the payment for such service as may be specified in the contracts made by its subscribers with such corporation, and the exclusion from such contracts of any charge made by a duly licensed chiropodist for treatment which he has furnished to any of the subscribers of such corporation is proper. Accordingly the order of the trial court in favor of the defendants was reversed. *Medical Care, Inc. v. Chiropody Association of West Virginia et al.*; 93 S. E. (2) 38 (W. Va., 1956).

MISCELLANY

This is the first part of a two-part article. The second part will appear in a subsequent issue of THE JOURNAL.—ED.

SOCIAL IN-SECURITY—THE TRAP AWAITING THE YOUNG M.D.

DON'T MISDIAGNOSE THIS SOCIAL DISEASE, IT'S CATCHING!

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Is your wife attractive? Do you love your children? Are you unhappy about higher income taxes? If your answers are "Yes," then you should invest the time to read on. Some scraps of paper and a pencil will allow you to determine for yourself whether social security will be a good value for you—or just an expensive delusion.

The authors of this paper are young men, one 34 and the other 37 years old. We have tried to answer for ourselves the following questions: 1. Would social security be good for my wife? 2. Would social security be good for my children? 3. Would social security be good for me?

We have searched for, found, and put together the figures necessary to allow us to make our decisions. We think that the formulas that we employed can be used by other physicians in making their own decisions about the prices or costs for them of social security and the possible values of it in their family planning.

TABLE 1.—*Social Security Taxes with Tax-Base of $4,200*

3% of $4,200 each year from 1956 through 1959 (4 years) 0.03 × $4,200 $126 × 4	$504.00
3½% of $4,200 each year from 1960 through 1964 (5 years) 0.0375 × $4,200 $157.50 × 5	$787.50
4½% of $4,200 each year from 1965 through 1969 (5 years) 0.45 × $4,200 $189 × 5	$945.00
5½% of $4,200 each year from 1970 through 1974 (5 years) 0.0525 × $4,200 $220.50 × 5	$1,102.50
6% of $4,200 each year from 1975 on 0.06 × $4,200 $252 yearly	Variable amount depending on how many years you keep earning

Guaranteed Costs—Social Security Taxes

At the time of writing, Jan. 12, 1956 (it is necessary to state the date for accuracy's sake, because both the social security tax rate and the social security tax base can be raised any day by Congress), you, as a self-employed physician, if you came under social security, would pay 3% on the first $4,200 of your yearly income for your social security taxes.

The social security tax rate has been set by law as follows: 1956 through 1959, 3%; 1960 through 1964, 3½%; 1965 through 1969, 4½%; 1970 through 1974, 5½%; 1975 on, 6%. If the tax base figure stayed at $4,200, you would pay the amounts shown in table 1 in social security taxes.

There are some facts you must know about the social security taxes under the present laws if you are to make decisions based on knowledge rather than on hope or faith. You must report your earnings and pay your tax each year when you file your individual income tax return. The money you pay the federal government in social security taxes is not a deduction as far as your income tax is concerned. In other words, if your net income was $4,200, you would pay income tax on the $4,200 and you also would be required to pay your social security tax on the same amount. There are no deductions allowing you to reduce your social security taxes. As long as you earn over $400 a year, you must pay social security taxes. This applies even after you are 65 years old, even after you are 72.

Possible Costs—Probable Increases in Social Security Tax Base and Tax Rate

One fact that is not advanced with the claims by the advocates of extension of social security to include physicians should give you real cause for concern. The social security tax base figure has risen 40% in just five years. In 1950, the maximum earned income you paid social security taxes on was $3,000. By 1955 it was up to $4,200. A proposal now before Congress would raise it to $4,800 this year. Absolutely nothing in the laws prohibits Congress from raising this figure each year.

Each physician should ask himself the following questions: 1. If I were a politician anxious to please the largest number of voters, would I favor raising the social security tax base figure so that more benefits can be promised? 2. How many votes will I lose by antagonizing those with incomes over $4,200? Over $4,800? Over $6,000? Over $10,000? 3. If I can promise more benefits to the lower income groups, how many votes can I pick up? 4. Since well over half of the voters earn less than $4,200 a year, isn't my course of action as a politician perfectly clear? The answers to these questions, and recent history, give you the probable, not just possible, future trend of the social security tax base figures.

You have no guarantee that the social security tax rate will not increase beyond the figures provided by the present laws. In fact, the Cooper bill, which promises increased benefits and which shot through the House of Representatives in 1955 by a vote of 372 to 31, would change the social security tax rates as shown in table 2.

Put yourself in the politician's shoes. This year, 1956, is an important election year. You read in the American Federation of Labor's *American Federationist* that the first real political test

TABLE 2.—*Social Security Tax Rates at Present and as Proposed in the Cooper Bill*

Present Law		Cooper Bill
Yr.	Rate, %	Rate, %
1956-1959	3	3⅝
1960-1964	3½	4½
1965-1969	4½	5½
1970-1975	5¼	6
1975 on	6	6¾

for the newly merged CIO and AFL labor giant will come on H. R. 7225, the Cooper bill. How would you vote? Can you think of any good political reasons for not increasing the social security tax rates even beyond the Cooper bill changes?

We could not. Therefore, in our determination of social security costs for the physician, we came to these conclusions: 1. The present laws guarantee that the social security tax rate will increase. (It was revised upward as recently as 1954, by the way.) 2. The 40% rise in the social security tax base in the last five years sets the historical pattern for similar increases of the tax base in the future. 3. Political expediency demands further increases in both the social security tax rates and tax base figures. 4. We're goin' to get 'em, sure as shootin'!

How high will they go? Your guess is certainly as good as ours; but, on the basis of a $1,200 rise in five years, the tax base figure would be $9,000 by 1975. Six per cent of that would equal a social security tax of $540 per year. Six and three-quarters per cent of $9,000 would be $607.50 per year. If you figure a 40% rise from the previous social security tax base figure every five years, your tax base figure would be $22,588.61 by 1979. Six per cent of $22,588.61 would equal a social security tax of $1,355.32 per year. If the tax rate had risen to 10% by then, the tax would be $2,258.86 per year.

A third way to estimate future costs, based on recent social security history, would be to add $600 each year to the tax base figure. In 1954, the first $3,600 of income was taxed. In 1955, $600 was added. A proposal before Congress now would add another $600 in 1956. Using this progression, the tax base figure would be $7,200 in 1960, $10,200 in 1965, $13,200 in 1970, and $16,200 in 1975. Six per cent of $16,200 would equal a social security tax of $972.

We all should recognize that the taxes may not be as high as these figures indicate—or that they might be higher. What the figures do show beyond a question of a doubt is that you cannot make any plans based on costs. And no one in the world can be certain of more accuracy in predicting the future social security tax rates or tax base figures or what you will actually pay in social security taxes each year than you can right now!

It should be recognized that a radical change has taken place in political thinking in the last few years. What applied in the early history of social security no longer can be used as the basis for future thinking. What was originally set up as a plan to provide a minimum of protection for the poor is now being extended into all phases of our social and economic body. The guiding principle in the 1930's was that social security should furnish a basic floor of protection against want in old age or in the survivors in the case of premature death of the breadwinner. Today, an enormous number of people whose chances of benefiting from the social security plan are essentially nil are paying compulsory taxes into the plan, and its proponents wish to extend its purse power into many other fields. In 20 years, coverage has increased from 33 million to 70 million people. New groups are being added, new promises are being made, and new taxes are following.

Lest you say that the costs cannot reach dangerously high levels, think of these facts. The "Minimum Standards of Social Security" convention, adopted by the International Labor Organization several years ago with the support of the labor and government delegates from the United States, includes greater old-age and survivors' benefits than we now have, disability benefits such as those proposed in the Cooper bill, weekly benefits for unemployment for any reason, benefits for maternity leave from the job, lump-sum job separation pay, and—compulsory health insurance.

Estimates indicate that such a program in this country would cost a minimum of 30% and as much as 40% of payroll. What is 40% of your net income before income taxes? The rate is 35% of much of France's payroll now. Some South American countries that have adopted just parts of the International Labor Organization's program have taxes running as high as 25% today.

It can happen here!

Possible Value of Social Security for the Younger Physician

Social security benefits have been touted to us, the younger men, in glowing terms. We have been told, "You can't buy cheaper life insurance," "Everybody else is on the gravy train, why shouldn't we hop on?" "Those old fogies in the A. M. A. made their bundles when they could salt it away; now they're the ones who are keeping us out." If ever physicians missed the boat on a diagnosis, we believe that this is it.

We think you will sense the injustice to our older colleagues as you read on. First, however, we must break the benefits into two main categories. You pay taxes toward both; but you or your family, in essence, can only collect one kind. For simplicity's sake, allow us to call them survivors' benefits and retirement benefits.

Survivors' Benefits—Are You Sure This "Cheap Life Insurance" Is Inexpensive?

We have heard repeatedly that, when we join the social security club, we get almost $37,000 of life insurance coverage. Perhaps you have been told the same thing. Were you also told that, to qualify for this maximum family coverage with the least expense, you first must pay maximum social security taxes for 18 months? The next day your wife must give birth to twins and you must die. Even the shock of twins is unlikely to cause this sudden demise on your part, but let us pretend that it does.

Your widow and twins would be paid survivors' benefits of $200 per month for 18 years, or $36,920. Unfortunately, there is some fine print. Your widow has to apply for the survivors' benefits. She may be attractive enough to remarry; but, if she does, she becomes ineligible to receive benefits. If either child marries, he gets no benefits. As soon as your twins become 18 years old, all benefits to them and to your widow stop. She gets nothing, then, until the age of 65, when she might become eligible to receive $81 per month.

If either child or your widow earns more than $1,200 per year, maximum benefits drop. If she or either of the twins earns $2,080.01 or more per year, no survivors' benefits will be paid

to the earner. If any one of the three earns over $400, he must pay social security taxes, though. Some other limiting "clauses" will be mentioned later, but let us get on with a cost comparison.

Most self-employed physicians earn at least $5,000 per year. Therefore, it is quite likely that you would have paid the maximum social security taxes for the 18 months before you died and the twins arrived. Using present figures and pretending that you came under social security at the beginning of 1956, you would pay $126 in 1956 and half of $126, or $63, in the first half of 1957. This would mean a "premium" paid of $126 plus $63, or $189, before your family could become eligible to receive any survivors' benefits. If the tax base figure is raised to $4,800 and the tax rate to 3¾, as is likely to happen this year, your "premium" would be $4,800 × 0.0375 = $180 for 1956 and half of $180, or $90, for the first half of 1957, a total of $270.

As a young physician, you can buy much better, guaranteed coverage for your family from private insurance companies. This you can do by purchasing decreasing term insurance (family income rider) without any other life insurance to guarantee your family $200 per month for 18 years. This maximum coverage goes into effect with the payment of your first premium. The yearly premiums would be $92 if you are 25 years old, $120 if you are 30 years old, and $164 if you are 35 years old.

An editorial in the Nov. 26, 1955, issue of THE JOURNAL of the American Medical Association cites premiums even lower than the figure we obtained. Their figures follow: $65 if you are 25 years old, $85 if you are 30 years old, and $115 if you are 35 years old. These figures from THE JOURNAL are the yearly premiums to establish monthly benefits of $200 for 20 years, 2 years more than the best that social security could do for your widow and twins. Here, these premiums would be in addition to those paid on a $20,000 ordinary life insurance policy. So few fathers are over 40 years of age when the last child is born that "a more realistic counterpart to the survivorship benefits for a widow with minor children" would be a 10-year "family income" clause for a physician 40 years old. The annual premium would be about $60. For a 45-year-old, the yearly premium would be only $83.

Thus, the twins that are born the day you die and your widow can qualify for maximum survivors' benefits if you have paid a minimum of $189 in social security taxes. Take your age and see what you would have to pay as your first premium for better coverage with private insurance companies. Should you really envy those already "lucky enough" to be in the compulsory social security plan?

Suppose, under either plan, social security or private insurance, you live until the twins reach age 18—and then you die. Unless your wife is 65 or over by that time, neither your wife nor your children would receive any payments in return for the money you have put in. How much would you have paid into the two systems during the period that they did have theoretical coverage?

Giving every possible benefit of the doubt to social security, saying that there will be no increases in the tax rate or tax base beyond those already certain under the old law, let us see what 19½ years of social security taxes add up to. Pretend that in the middle of 1956 doctors come under the social security system on a compulsory basis. You will pay $63 for half of 1956, $126 from 1956-1959 (in 1958 you become eligible and your twins are born); $157.50 from 1960-1964; $189 from 1965-1969; $220.50 from 1970-1974; and $252 in 1975. If you die at the beginning of 1976, your absolute minimum social security tax will have been $3,528.

With private insurance, according to our figures, which are less favorable than those cited in THE JOURNAL, your costs would be 18 × $92, or $1,656, if you became 25 years old the day the twins were born, 18 × $120, or $2,160, if you became 30 years old on that day, and 18 × $164, or $2,952, if you became 35 years old on that day. Note that the younger you are the less you pay.

According to the figures given in the editorial in THE JOURNAL, your costs, according to your age the day the twins were born, for 20 years of guaranteed coverage of $200 per month (2 years or $4,800 more coverage than social security offers) would be 20 × $65, or $1,300, if you were 25 years old the day the twins were born; 20 × $85, or $1,700, if you were 30; 20 × $115, or $2,300, if you were 35; and 20 × $166, or $3,320, if you were 40. Compare these figures with the $3,528 you know you would have to pay under social security (remember that this is the absolute minimum, not the much more likely higher figures). Does social security "insurance" sound so inexpensive now?

Before we leave this "twin situation," please let us indicate the further cost of one of the hidden factors in social security. Bear in mind that the private insurance costs end 18 or 20 years after the twins are born. It is crucially important to remember that your social security taxes continue each year that you earn over $400. Since only one doctor out of seven between the ages of 65 and 75 is retired, it is unlikely that you will retire. In fact, as you will see later, it may be impossible for the younger physician to retire. If you earn over $2,080, you can get no retirement benefits until you are 72 years old. So let us take the case of the young physician who had the twins and who lives to age 72, and then dies. He has a 6/7 chance of having earned until he dies and hence a 6/7 chance of paying social security taxes until then.

Again using the unlikely but most favorable social security figures without the expected rise in tax rate or tax base figures beyond those of the present law, let us see what his social security taxes would be.

Pretend that the twins were born at the beginning of 1958 and that the physician has been paying taxes into social security for 18 months. This year of 1958 is picked to slant the figures in favor of social security, since the taxes are lower in the earlier years.

If he were 25 years old the day the twins were born, he would have paid a total of $3,528 plus $7,308, or $10,836, in social security taxes. For that amount of money, he could have bought over six times as much private insurance for his wife and twins, or over $1,200 per month guaranteed income for them. These amounts are arrived at using our figures for the insurance premiums, not the more favorable ones from THE JOURNAL.

If the physician were 30 years old the day the twins were born, he would pay social security taxes of $3,528 plus $6,048, or $9,576. With that he could have bought four times as much private insurance coverage for his wife and twins, or over $800 per month of guaranteed income for them for 18 years. The figures for age 35 are $3,528 plus $4,788, or $8,316. With that he could have bought over two and one-half times as much coverage, or over $500 per month of guaranteed family income.

On the basis of the figures from THE JOURNAL for the insurance premiums, the physician, age 25, would pay $1,170 in 18 years. He could have stopped his payments at the end of 18 years. Under the social security system, he would have been taxed a minimum of $10,836 by the time he was 72. For that amount he could have bought over nine times as much coverage for his family.

According to premium figures in THE JOURNAL again, the physician, aged 40 at the time the twins were born, would pay $2,988 for 18 years of family income protection. At age 72 he would have paid, under the social security system, $7,056. He could have bought two times as much protection for his family using available private insurance plans.

We have spent all this time comparing private insurance premium costs and social security tax costs for the unlikely twin situation because it is only under these conditions that you could get the maximum coverage from social security. This is the bonanza that seems so attractive to many of the younger doctors.

From a practical point of view, there is almost no chance for your family to collect the theoretical maximum benefits described so far. Your chances of dying just 18 months after you begin paying social security taxes and of your wife's having twins on that same day are about nil. It is time now to get into the realm of the more likely situations. How, then, would you determine comparable costs and possible values of the two systems under your own, actual, personal family circumstances?

No matter what your family circumstances, once you come under compulsory social security, you pay the taxes. Pretend that the starting day was the beginning of the second half of 1956. You will pay the taxes, as mentioned previously, until the beginning of 1958 before you become eligible for survivors' benefits. If you have paid and continue to pay maximum social security taxes, your youngest child, your next-to-the-youngest child, and your widow might be paid $200 a month of survivors' benefits until your next-to-the-youngest child reaches age 18. The social security maximum coverage per dollar put in by you that they

could get would be paid if you died at the beginning of 1958. Determine for yourself the age of your next-to-the-youngest child at the beginning of 1958. Subtract that age from 18. This will give you the number of years of possible $200 monthly payments.

Now determine the age of your youngest child at the beginning of 1958. Subtract this age from the age of your next-to-the-youngest child at the beginning of 1958. This figure will tell you the number of years that your widow and youngest child might be paid a maximum of $162.80 per month after your next-to-the-youngest child became age 18 and the $200 monthly payments stopped.

You now have the means of determining what your maximum family coverage might be. Take the number of years of $200 monthly payments and multiply this figure by 12 times 200. Now add the number of years of $162.80 monthly payments by 12 times 162.80. The sum is the maximum family coverage that you can hope for from social security.

Divide this figure by the number of years that would elapse between the beginning of 1958 and the time when your youngest child becomes 18. This will tell you what your family might receive per year until your youngest child becomes 18. Divide this figure by 12 and you will have their possible monthly income from social security survivors' benefits, should you die at the beginning of 1958. Now call your insurance man and ask him what comparable private insurance coverage under a family income rider would cost you. We think you will be pleasantly surprised.

You can get a rough idea if you know the following: For 18 years of private guaranteed coverage for your family, your yearly premiums per $1,000 of initial coverage beginning at age 25 would be $2.50. At age 30, your yearly premium per $1,000 of coverage would be $3.25. If you started with this 18-year plan at age 35, you would pay $4.43 per $1,000 of coverage. At age 40 you would pay $6.40 per $1,000 of coverage. You do not have to have any other life insurance to get these premium figures.

Obviously, most of you will find that you will not want 18 years of coverage or, at least, that social security would not give you 18 years of coverage, because your youngest child would be older than one day at the beginning of 1958.

The figures cited in THE JOURNAL indicate that, to get $200 coverage a month, a physician beginning a 10-year family income clause at age 40 would pay an annual premium of $60. At age 45, a 10-year guaranteed $200 monthly income for your family would cost $83 per year. Thus, for $24,000 of initial coverage beginning in these age groups, the yearly premiums would be $60 and $83 respectively. The yearly premium per $1,000 coverage would be $2.50 for the 40-year-old physician. For the 45-year-old physician, it would be $3.46.

Having derived a rough estimate of your yearly premium, or an exact one from your insurance man, compare your premium costs with your costs in the social security scheme (the tax figures mentioned earlier in this article). The observation is apparent immediately that the younger you are, the more you have to lose by being forced into the compulsory social security system!

Hidden Hookers in Social Security Survivors' Benefits

You must die in either the private insurance plan or the social security survivors' benefits plan for your family to collect any benefits. But in most respects, the resemblances end here. We have mentioned that your wife cannot remarry. Your children cannot get married before age 18. As soon as the youngest child becomes 18 years old, all payments under social security stop. Your widow would not get anything until age 65, when she might become eligible to receive $81.40 per month. None of the three can earn more than $1,200 per year without a drop in the maximum benefits. No one can earn over $2,080 if he or she is to receive any survivors' benefits.

Keep in mind that a compulsory social security system for physicians would force all physicians to pay social security taxes. The taxes would be the same whether you had any dependents or not. If you are unmarried, a dependent parent aged 65 or over could receive social security survivors' benefit payments after your death. The maximum monthly payment to a dependent parent, age 65 or over, is $81.40. If your wife survives you and you have no children, she is entitled to no survivors' benefits until she reaches age 65. Some doctors' wives have careers of their own. If so, they are probably ineligible for survivors' benefits; and, in fact, they almost certainly would continue paying social security taxes. In brief, you would pay the social security taxes whether you had any chance to benefit from the payments or not. No matter how your family circumstances change, you still pay the compulsory tax.

It should be noted that these are just some of the limitations. There are others, but you need to be a lawyer to dig them all out. The benefits are not paid automatically on your death. The beneficiary must know he is a beneficiary and must apply for benefits. It is interesting to note that many possible beneficiaries never get around to applying for the benefits.

The amount of the benefit payment is determined in each case by various formulas. For those who earn something, the following directions are printed in a social security booklet "simplifying" the laws for the layman: "There is no single rule for determining whether a person is performing substantial services in self-employment. There are many factors to be considered for different kinds of trades and businesses. The social security administration will make decisions based on the particular facts in each case." Does this sound exact enough for you to bank on in planing your family security? What does your widow do when she runs into the "fine print"?

Retirement Benefits—What They Are and How You Become Eligible for Them

If you retire at age 65 or thereafter and are eligible, you and your wife may be paid retirement benefits. You must survive to collect. If you are eligible, alive, retired, age 65 or over, and have paid maximum social security taxes long enough, you can receive $108.50 per month under the old-age benefits. You and your wife, if she is alive and age 65 or over, can receive $162.80 per month. If your wife survives you, and she is age 65 or over, she can be paid $81.60 per month. These are the maximum figures.

To become eligible, you must fit into any one of these three categories: 1. You must have worked under social security and paid taxes for a total of at least 10 years. 2. All the months that you have worked under social security at any time, when added together, must equal at least half the time between Jan. 1, 1951, and the date you reach age 65. 3. You must have worked steadily under social security through every quarter from Jan. 1, 1955, to the date you reach age 65.

For most young physicians, the requirement of import would be that they work under social security for a total of at least 10 years. However, if compulsory social security for physicians began in the middle of 1956, obviously most would work a good many more than 10 years under social security before reaching age 65. In fact, most who survive to the "golden age" will continue working. If they earn over $2,080, they will not be eligible to receive retirement benefits until age 72. Then, whether they retire or not, they are eligible to receive the benefits. But, if they continue earning over $400 a year beyond age 72, they pay social security taxes on their earnings.

Retirement Benefits—What Is the Young Doctor's Chance of Collecting?

The young doctor's chance of collecting retirement benefits is very poor!

You must survive to age 65. To collect maximum monthly retirement benefits, you and your wife both must survive and you must both be 65 or over. To collect any retirement benefits, you must earn less than $2,080.01 a year—at least until you reach age 72. To collect maximum retirement benefits, you must earn less than $1,200 a year until age 72.

How likely are you to survive to age 65? If you are 20 years old now, your chance of surviving to age 65 is 61%. If you are 25, your chance is 62%. If you are 30, your chance is 63%. If you are 35, your chance of surviving to age 65 is 64%. If you are 40, the figure is 65%. If you are 45, your chance is 68%.

Thus, the odds are that, of three younger physicians (under 45 years of age), one will never reach 65. Your wife's chances are about the same. But the chances are much less than two to three that you and your wife will both reach 65. In fact, they are less than 50%.

The younger you are, the less chance you have. Again, we see that the older physicians have less to lose or more to gain than the younger man. A man age 55 has a 77% chance of reaching 65. A man age 60 has an 85% chance of reaching 65. Have our older colleagues really been misleading us? So far, the figures do not bear out the charges.

Now, let us pretend that you are in the lucky two-thirds. You reach age 65. The most recent figures show that only one doctor in seven in the age group 65-75 is retired.

If you are willing to accept these figures, you have about 2/3 x 1/7, or 2/21, or less than a 10% chance of collecting any retirement benefits from social security before age 72. To collect the maximum retirement benefits of $162.80 per month, both you and your wife must survive. You and your wife have about 2/3 x 2/3 x 1/7, or 4/63, or less than a 7% chance of collecting the maximum monthly benefit.

You could say that the number of doctors retired today has no bearing on the percentage that will retire in the future. However, the chances are that, the younger you are now, the more difficult it will be for you to retire in the future, even if you wanted to retire at age 65. The younger you are, the longer your training has taken. The younger you are, the more dollars your training has cost. We all know the history of income and other taxes. How do you, the young physician, get enough money put aside to retire on? Can you say that $162.80 per month will suffice to keep you and your wife comfortable 40 years from now (if you are age 25 now), 20 years from now (if you are age 45 now)? Remember that one dollar 20 years ago is today worth only about 50 cents. What will $162.80 be worth 20 years from now? Forty years from now? If $162.80 per month is not enough to keep you and your wife comfortable when you reach age 65, you may have to stay in practice. How do you, in practice, keep your earnings under $2,080 per year? If you don't, you won't get any social security retirement benefits.

Almost every indication is that, with increasing lengths of time required in training, the physician's earning years will be shorter in the future. Thus he will have to earn more per year. If he earns more, graduated income taxes take bigger bites. If the income tax rates rise, and there are reasons, as you will see later, to suspect that they will, then the tax bite will be greater still. If living costs rise, money left over for the future retirement will be harder to come by. If the dollar continues losing its value (inflation), any money you can manage to put aside will purchase less at retirement age. With these factors in mind, what do you think about your chances for retirement? Will they be greater or less than those of the physicians age 65 or over today?

If you do not retire, you will be paying the social security taxes, whatever they might be by then, long after most formerly employed people in other occupations have stopped paying them and have started collecting their retirement benefits.

In essence, that part of your social security tax dollar going toward retirement benefits, with today's figures (favorable to social security), would be split about like this: over 90 cents of it is likely to go to pay for other peoples' retirement benefits; you are likely to get back less than 10 cents.

Costs for Retirement Benefit Coverage

Earlier in this article we indicated the tax costs of social security coverage. These figures apply to retirement benefits, also. Again we find that, the younger the physician, the higher the costs are likely to be. The doctor, age 35 at the beginning of a compulsory social security system for physicians, would only have to pay the social security taxes for 10 years before reaching age 65. The younger you are at the beginning of a compulsory system, the more social security tax years you face before you reach age 65. The present laws guarantee a rise of the social security tax rates and of the tax base figures. We have indicated that the known figures are likely to be raised well beyond the presently known rates of increase. If you will look at the earlier figures, you will find that they support these statements. Suffice it here to say that the greatest costs will be inflicted on the younger physicians.

To be realistic, in comparing costs of social security and of private retirement plans, you, as a young doctor, should decide what your chances for actually retiring are. We believe your chances of retiring are less than one in seven, for reasons just mentioned. However, let us pretend that they are one in seven. Since private plans guarantee payments whether you are retired or not, they are seven times more valuable to you; or, said another way, social security is one-seventh as valuable as far as retirement benefits go. Now let us look for costs of a private plan that would pay benefits equaling one-seventh of the theoretical maximum social security retirement benefits. To get the maximum social security retirement benefits, both you and your wife must be age 65 or over. Therefore, in deriving the figures to be listed for the private plan, let us assume that you and your wife are the same age.

Annual premium payments for a private annuity deferred to age 65 providing a monthly income of one-seventh of $162.80 while both you and your wife are living, one-seventh of $108.50 per month while you alone live, and one-seventh of $81.50 per month while only your wife lives would be $60.52 if you are 25 years old at the start, $74.05 if you are 30, $92.59 if you are 35, $119.24 if you are 40, $160.27 if you are 45, and $230.29 if you are 50.

The one-in-seven thinking no longer applies after age 72. Then, if you have made maximum contributions to social security for the required time, you and your wife, both age 72, can collect maximum social security retirement benefits. A telephone call to your insurance man will get you the annual premium figures for you and your wife at your own present ages for an annuity deferred to age 72 paying benefits comparable to those that social security promises. Believe us when we say that this premium figure will be less than seven times the annual premium figures mentioned just before. Yet for six-sevenths of the doctors this is the cost figure that should be of most interest in comparing real values of the two systems. This is the figure that should be compared with what you guess your total social security taxes will amount to in the years ahead until you reach age 72. This is the time to go back to the earlier figures relating to social security taxes and the observations connected with them.

While we are still on the subject of taxes, you might be interested in knowing that once under compulsory social security, the physician and his wife could only arrange a maximum tax-free yearly income, after age 65, of $5,503.59. As long as you can stay out of the social security system, you and your wife can arrange a maximum yearly tax-free retirement income, after age 65, of $18,148.48. This you can do with retirement income policies and stocks paying dividends.

Retirement Benefits Versus Survivors' Benefits—One at the Expense of the Other

While you still have a choice about compulsory inclusion of physicians under social security, it behooves you to think clearly about costs and values. If you are an insurable younger physician, you probably are much more interested in getting protection for your wife and children in case of your early death than you are in the retirement benefit parts of social security.

We have shown previously that you can buy much more insurance for family protection from private insurance companies than you can get from social security for the same amount of dollars contributed in the form of social security taxes. Remember, you have no cash value to tap for family or personal emergencies in social security as you do with many kinds of insurance. Since so much of your social security tax dollar goes toward retirement benefits, your goal of family protection becomes harder to achieve, not easier.

You might justify this in your mind by saying that part of your family goal is to arrange things so that you and your wife will not be dependent on your children in your old age. With such a small chance that the money you are putting into social security will ever be used for your retirement, with a greater than 90% chance that it will be used for other peoples' retirements, are you really looking out for your family properly?

Remember, you cannot collect both survivors' benefits and retirement benefits. It's one or the other—and because you are a physician, it is likely to be neither!

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THE LEISURE CORNER

THE DOCTOR WRITES A LETTER

Although doctors have at all times incurred the abuse of nonmedical people, they have also received almost extravagant praise. Much truth has been said in jest—and much untruth as well. Still, no other group of professional men and women can show a greater personal sacrifice, a greater devotion to duty, and a sounder consideration for the welfare of humanity. Throughout the centuries, evidence of this has been expressed in personal letters written by doctors to their colleagues, their patients, and to organizations with which they have been affiliated, whether professional, social, or political. Many well-known doctors, whose medical achievements are unrivaled during a busy professional life, often fail to contribute their experiences to the general medical literature. However, they do sometimes sit down and write to a colleague a revealing letter, the kind that makes medical history. In this connection, the first mention of the use of the stethoscope by Rene Laënnec was made in a letter to his cousin. "My cylinder is a real find," he wrote. "Too bad it wasn't hit upon by certain people who would have known how to make a lot of money out of it. As for me, I'm only a fool in such matters, and I will not get more out of it than a little smoke which, to my further detriment, I will not estimate for more than it is really worth." Twenty years later Laënnec was acclaimed for his contribution to medicine.

The decision of a doctor to retire from medical practice has much to do with the state of his physical and mental powers as well as with his individual needs and circumstances. To set an age limit for retirement may seem a little absurd in view of the past accomplishments of older men and women in the practice of medicine. There is no doubt that for originality and vigor younger physicians hold an advantage, but for wisdom and judgment, mature age often holds a distinct advantage. When a doctor reaches the age of retirement, he, like others, would like a feeling of security, with the knowledge that many of the pressing difficulties of life have been overcome. Despite this objective, it may be difficult to know precisely when to reach a decision for voluntary retirement. On the other hand, it is painful and somewhat tragic to witness the slow disintegration of those who have hung on too long in medical practice. Harvey Cushing, the great brain surgeon, once wrote a letter to his friend Dr. Henry Christian of the Peter Bent Brigham Hospital, Boston, expressing some thought on the subject of retirement among doctors.

"Why not put the surgical age of retirement for the attending surgeon at sixty, and the physician at sixty-three or sixty-five, as you think best? I have an idea that the surgeon's fingers are apt to get a little stiff and thus make him less competent before the physician's cerebral vessels do. . . . Then, of course, many of us get, vascularly speaking, a little inelastic well on the side of sixty, or may remain in this respect as youthful at seventy as others are at fifty. This is all a lottery of inheritance and habits, and I shall be very glad, for one, to have legislated to stop active work at sixty."

While many doctors carry on a medical practice at the age of 70, they usually do so on a limited scale. They are philosophical about their semiretirement, knowing there is little point to cracking hazel nuts with dentures. Semiretired physicians do not dislike the world they live in, nor do they assume an attitude of indifference. This point of view was effectively stated in a letter written by Dr. Frederic C. Sharpless to the editor of THE JOURNAL of the American Medical Association a number of years ago: "It is my impression that few doctors retire voluntarily, and, of those who do, few live happily ever after. The usual pattern is that the doctor, if he lives long enough, does not give up his patients; the patients give up their doctor. . . . At the same time he must be aware of the let-down that will come when he is deprived of the daily interest and sense of importance that medical life so abundantly provides."

If doctors have interests outside of the field of medicine and if, through necessity or training, they are able to apply their talents as did Anton Chekhov in his brilliant literary accomplishments, it is always of great interest to learn just what started them off in the new fields of endeavor. Anton Chekhov loved to write letters to his friends. In fact, many of them, aware of his great literary talent, urged him to give up the practice of medicine and to devote all his time to literary work. Chekhov, however, realized that his medical background played an important role in making him an effective writer. He always liked to think that he had two professions at his command—medicine and literature. In a letter to a friend he stressed how important his medical background had been to him as a writer: "I have no doubt that the study of medicine has had an important influence on my literary work; it has considerably enlarged the sphere of my observation, has enriched me with knowledge the true value of which for me as a writer can only be understood by one who is himself a doctor. It has also had a guiding influence, and it is probably due to my close association with medicine that I have succeeded in avoiding many mistakes."

Among the factors that make some people turn away from intelligent physicians and place their trust in imposters is the delusion that physicians know everything and should effect cures immediately, like a magician. Again, some lay people hold that physicians should always use pleasant methods of treatment, procedures that are not at all times and in all cases possible. As patients are educated to obtain a reasonable understanding of disease, it has been the hope of most physicians that a better informed public would eventually grasp the essence of fake practices in medicine. Years ago Oliver Wendel Holmes wrote a letter to the New York Academy of Medicine about the intrusion of the quack into medical practice and the apparent willingness of some of the public to fall into his hands.

"The public is so ready, so eager to be deceived and the traders in deceptions are so willing, so hungry to deceive those who will listen to them that it needs a solid wall of resistance, a close united phalanx of men of recognized sense, knowledge and character to stand against them. . . . The Medical Profession will always have to fight against the claims of wrong-headed, and too often dishonest individuals and "schools" as they call themselves. . . . Long may it be before the wholesome barriers are weakened that separate the thoroughbred and truly scientific practitioner from the plausible pretender with his pseudopathy and his pseudotheraphy."

When a patient is sick and dispirited, a malignant disease is a very bitter pill to swallow. There have been several schools of thought as to whether patients should be told that they are suffering from an incurable disease. Times like these are also most difficult and trying for a physician. With respect to the problem, Dr. Johann Stieglitz, a highly respected German physician, wrote to a young medical friend in the early part of the 19th century:

"One can frequently hear people say that they do not fear death but are afraid of dying. . . . I have often thought it would be important to instruct physicians how to behave in cases of incurable disease, not so much to tell them what to do, but what not to do.

"I am often outraged when, in cases of large tumors, of carcinoma, of unquestionable protracted glaucoma and in innumerable instances, I see elaborate therapeutic plans being developed when no one can doubt that the disease is uncurable. . . . The patient often wishes to be told clearly whether he must be expected to die and whether death now be inevitable.

"Reasons are offered to show how important it would be to have this information and to prove with what fortitude and resignation he would be able to accept it. The physician may never take away all hope. . . . Man doesn't want others to inequivocally express even what is perfectly clear to him if it is of evil nature and affects him. He still wants to be able to believe that the contrary may be possible."

Many patients have been offered valuable medical advice in letters written to them by their doctors. Over a span of two and a half centuries, letters written by doctors have clearly reflected the existing status of medical practice. The complete evolution of medicine as known today can be traced through letters only because physicians enjoyed the personal pleasure of putting their experiences down on paper.

Letter sequences can be as exciting as sonnet sequences and a great deal more revealing. By reading letters written by physicians, it is possible to trace both the medical annals of the past and medical history in the making. In their letters, physicians frequently reveal sources of deep emotions, hidden up to that time from the public eye. Actually, it is only in a personal letter that the hidden springs of conduct may be revealed. A doctor will live in his letters as only a doctor likes to think he can live—a life of challenge and a life of critical self-examination.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Treatment of Chronic Congestive Heart Failure with Neohydrin for from Eight to 65 Months. G. C. Griffith, S. P. Dimitroff and M. C. Thorner. Ann. Int. Med. 45:7-13 (July) 1956 [Lancaster, Pa.].

Chlormerodrin (Neohydrin) has been described as one of the most efficient organomercurial diuretics available for oral administration. The authors evaluate its effectiveness in patients who received the drug daily for periods of up to 65 months. In view of the widespread belief that the principal toxic effects of organomercurial diuretics appear in the kidney, special attention was directed to this organ for evidences of injury. Twenty-three patients who had had chronic congestive heart failure for from 7 months to 18 years were studied. They were seen in the adult outpatient cardiac clinics of the Los Angeles County Hospital and also in private practice. More than half were over 60 years old. Arteriosclerotic heart disease was the most common entity, although a significant number had inactive rheumatic heart disease. Hypertension and cor pulmonale were also represented. The patients were given Neohydrin tablets, each containing the equivalent of 10 mg. of organic mercury. The daily dose varied from one to three tablets. Other indicated medication, such as digitalis preparations, low-sodium diet, and, occasionally, aminophylline, was included in the therapeutic regimen along with Neohydrin.

Observations on these patients confirmed the efficacy of the drug. Histological study of the kidneys was possible in one patient who initially had severe congestive heart failure with albuminuria and high nonprotein nitrogen values. He had received two tablets of Neohydrin daily for nine months. The congestive symptoms were controlled, and the renal abnormalities disappeared. He suddenly died of acute right heart failure. Postmortem examination showed normal kidneys except for passive congestion. There was no tubular damage. Thus albuminuria and high nonprotein nitrogen values are not necessarily a contraindication to treatment with this oral organomercurial diuretic. Neohydrin, however, is definitely contraindicated in the presence of primary renal disease. Active digestive tract disease and allergy are the other contraindications. The authors conclude that patients without primary renal disease but with albuminuria and high nonprotein nitrogen due to congestive circulatory changes can be adequately and safely treated with Neohydrin for long periods of time.

The Effectiveness of an Oral Vitamin K$_1$ in Controlling Excessive Hypoprothrombinemia During Anticoagulant Therapy. S. W. Cosgriff. Ann. Int. Med. 45:14-22 (July) 1956 [Lancaster, Pa.].

During the last year Vitamin K$_1$ in tablet form has become available for oral use. This drug, in doses of 2.5 to 20 mg., was administered to 75 patients in whom excessively elevated prothrombin-time values were produced by anticoagulant therapy. The coumarin or indandione drugs must be used in sufficient amounts to prolong the prothrombin time into the therapeutic range wherein an antithrombosing effect is produced but in which there is little risk of hemorrhagic complications, i. e., "safe but adequate" anticoagulation. At the laboratory of the author the therapeutic range for treatment of a patient with an acute thromboembolic problem is considered a prothrombin time between 22 and 35 seconds. It has been demonstrated that no further beneficial antithrombosing influence accrues when the prothrombin time rises above 35 seconds. Moreover, the majority of hemorrhagic complications occur in association with prothrombin-time values above this level. Consequently, it seems advisable to reduce a prothrombin time that has been elevated above 35 seconds as soon as possible to the safe therapeutic level, even though no bleeding has occurred. It has been customary at the author's clinic to administer water-soluble vitamin K parenterally or vitamin K$_1$ orally whenever the prothrombin time rises above 35 seconds.

In 63 of the 75 patients who were given vitamin K$_1$ in tablet form, the prothrombin time returned to the safe range (35 seconds or less) within 12 hours after oral administration and in all but 2 of the patients within 24 hours. The prothrombin time fell below the lower therapeutic level of adequate anticoagulation in 11 of the patients at 12 hours after the administration of vitamin K$_1$. Under such circumstances the administration of heparin ensured a continuing antithrombotic effect until subsequent doses of a coumarin or indandione agent again produced an adequate hypoprothrombinemia. Vitamin K$_1$ tablets for oral use provide an additional safeguard in coumarin and indandione therapy.

Postcardiotomy Syndrome in Patients with Rheumatic Heart Disease: Cortisone as a Prophylactic and Therapeutic Agent. D. T. Dresdale, C. B. Ripstein, S. V. Guzman and M. A. Greene. Am. J. Med. 21:57-74 (July) 1956 [New York].

In 33 (39%) of 84 patients with rheumatic heart disease who underwent cardiac surgery, a syndrome developed that was characterized by fever and, in descending order of frequency, chest pain of a pleuropericardial nature, congestive heart failure, pleural effusion, polyarthritis, arrhythmia, abdominal pain, and subcutaneous nodules. Laboratory evidence indicative of a nonspecific inflammatory process was frequently present. This increased the immediate postoperative morbidity and also that at a later date, at which time it usually incapacitated the patient. Death occurred in two patients; one died shortly after the intravenous administration of morphine, and the immediate cause of death was not clear. Autopsy did not reveal any evidence of rheumatic activity. Florid rheumatic myocarditis was revealed by autopsy in the other patient. Terms such as postcommissurotomy syndrome, reactivation of rheumatic fever following mitral commissurotomy, and postvalvulotomy syndrome have been used by other workers to describe this syndrome, but the authors prefer the designation "postcardiotomy syndrome in patients with rheumatic heart disease" because they observed the syndrome in a patient in whom only cardiotomy was performed and mitral valve surgery was omitted because of technical difficulties. It seems, therefore, that mitral commissurotomy is not necessary for the development of the syndrome. It is suggested that the postcardiotomy syndrome occurs in patients with rheumatic heart disease because of trauma to the heart or pericardium, which was the site of rheumatic activity at some time in the past.

For the purpose of studying the prophylactic use of cortisone postoperatively, the 84 patients were divided into two groups. Fifty-eight patients received cortisone within the first two postoperative days and were maintained on cortisone for from three to eight weeks thereafter. Doses of cortisone ranged from 150 to 300 mg. daily for the first two weeks and from 75 to 150 mg. for the next one to six weeks. The remaining 26 patients were not given cortisone postoperatively and served as controls. Cortisone had a definitely suppressive effect on the postcardiotomy syndrome. Eight (31%) of the 26 patients who did not receive cortisone prophylactically during the immediate postoperative period had the postcardiotomy syndrome during the initial three to eight weeks after the surgical intervention. In only 4 (7%) of the 58 patients who received cortisone prophylactically did the syndrome develop during a similar period while they were taking cortisone. The incidence of the postcardiotomy syndrome, however, was similar in both groups (8 [31%] of the 26 patients, and 17 [29%] of the 58 patients) after the initial postoperative

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The place of publication of the periodicals appears in brackets preceding each abstract.

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period of from three to eight weeks, when cortisone was withdrawn in the 58 patients. The immediate postoperative course of patients who received cortisone prophylactically was less stormy than that of those who did not. As a therapeutic agent, cortisone was superior to salicylates, aminopyrine, and antibiotics, none of which had a favorable effect on the clinical manifestations of the postcardiotomy syndrome. Cortisone in doses varying from 50 to 300 mg. daily, depending on the individual patient, caused a dramatic remission of symptoms and fever in the postcardiotomy syndrome. Because of the decreased immediate postoperative morbidity when cortisone was given prophylatically, and because corticotropin (ACTH) had an effect similar to that of cortisone on the symptoms of the postcardiotomy syndrome, the authors recommend that corticotropin (ACTH) be given prophylactically for two days preoperatively and for 8 or 10 days postoperatively to patients with rheumatic heart disease who are undergoing mitral valvulotomy.

Early Diagnosis of Bronchial Carcinoma. H. W. Knipping, E. Liese and A. Schmutte. München. med. Wchnschr. **98**:937-941 (July 13) 1956 (In German) [Munich, Germany].

The authors, who reported in 1951 on early signs of bronchial cancer in 150 patients, present here observations on 180 additional patients. Early recognition is the crucial point in bronchial cancer, because long-term therapeutic results have remained unsatisfactory despite the great advances in thoracic surgery. A series of special examinations must be carried out whenever there is even the slightest suspicion of bronchial cancer. These examinations include bronchoscopy, bronchography, cytological tests, and exploratory thoracotomy. However, suspicious signs are frequent in persons of certain age groups, and those who have them often regard them as trifling and refuse to submit to the rather exhausting examinations; at any rate, they are not inclined to submit to them repeatedly, the less so since only a small proportion of those who exhibit the early suspicious signs actually have bronchial cancer. For this reason, methods are required that can be carried out without causing too much inconvenience, so that the patient will submit to them repeatedly. In patients in whom bronchial cancer seems highly probable and in whom a surgical intervention is planned, bronchoscopy and bronchography should always be employed.

The authors feel that the most important method of preliminary examination is body-section roentgenography (tomography), particularly with the improvements they have introduced. The newest form of this body-section roentgenography is simultaneous multilayer tomography, which is explained with the aid of a diagram. This improved method can now be employed for routine examinations. Other diagnostic methods are bronchography with the aid of either radioactive iodine-alkyl or with radioactive xenon. These methods have proved useful in routine clinical work. Another important development in the early diagnosis of bronchial carcinoma is bronchography on the basis of the visualization of the distribution of radioactive xenon in the blood vessels and air passages. This method also enabled the authors to accomplish a direct demonstration of the moving heart (in situ and in vivo) without the aid of the roentgen apparatus (angiocardiography with the aid of isotopes). They also describe further improvements and developments aimed at the development of isotope bronchography. The use of isotopes, particularly of radioactive xenon, as employed by the authors in the diagnosis of cardiac and pulmonary disorders involves no inconveniences for the patients.

The Early Diagnosis and Natural History of Chronic Lymphatic Leukemia. C. Hougie. Ann. Int. Med. **45**:39-53 (July) 1956 [Lancaster, Pa.]

Chronic lymphatic leukemia may run a long and practically asymptomatic course. The classic picture of splenomegaly, lymphadenopathy, anemia, and a very high leukocyte count is probably only a late phase in its natural history. The nine patients with chronic lymphatic leukemia described here were all first seen with presenting symptoms not attributable to leukemia and are of interest because of the light they throw on the natural history of the disease. Three of these patients died from causes unrelated to the leukemia shortly after the diagnosis of chronic lymphatic leukemia was established. Autopsies were performed on two of these. The lymph nodes in both patients showed no histological changes suggestive of leukemia, although well-marked lymphocytic infiltration of the portal tracts of the livers and extensive lymphocytic infiltration of the bone marrows were present. The spleen was not enlarged and showed no abnormal histological changes apart from congestion. Lymph node biopsy was performed at a relatively early stage of the disease in three of the remaining patients; these nodes showed no leukemic changes, while a splenic biopsy performed in one of the patients showed no leukemic changes. Lymph node biopsy is apparently of no value in the diagnosis of early chronic lymphatic leukemia. The leukocyte counts were below 45,000 per cubic millimeter in all but one of these patients. From other early cases described in the literature it appears that the leukocyte count usually remains low for several years and that anemia and thrombocytopenia are late manifestations of chronic lymphatic leukemia.

It is postulated that there are no signs or symptoms in the first stages of chronic lymphatic leukemia and that this "silent" phase of the disease lasts many years. It is succeeded by a phase, also of many years' duration, in which there are signs of the disease but no symptoms. The classic picture of the disease, with anemia, gross splenomegaly, lymphadenopathy, thrombocytopenia, and a very high white cell count, is considered to be only the terminal phase of a disease that usually runs a course lasting from 10 to 20 years.

Which Nodular Goiters Should Be Removed? M. Perlmutter and S. L. Slater. New England J. Med. **255**:65-71 (July 12) 1956 [Boston].

The authors present a physiological plan for the diagnosis and treatment of nodular goiter. A review of the literature indicates that clinically palpable thyroid nodules are present in from 4 to 12% of the population of the United States. The incidence of cancer in unselected nodular goiters may be as high as 2 to 5%; in surgically treated multinodular goiter it is 3 to 10% and in uninodular goiter 9 to 33%. Most evidence indicates that benign thyroid nodules rarely undergo malignant transformation, and therefore surgical therapy as a prophylaxis against carcinoma is not indicated. Excisional therapy is indicated for nodules that are considered likely to be carcinomatous. Evaluation of thyroid nodules for malignancy or benigancy is performed on patients of the endocrine clinic of the Maimonides Hospital who have nodules that are clinically benign by means of laboratory determination of the total 24-hour uptake of radioactive iodine (I^{131}) by the thyroid gland. In patients with uninodular goiters (and those with masses restricted to one lobe), directional counts are made over the various parts of the gland, and the uptake over the nodular area is compared with that over the presumably normal parts of the gland. By definition, a "hot" (very probably benign) nodule is one that concentrates at least 125% as much I^{131} as the non-nodular portion of the gland. A nodule that concentrates less than 125% is considered "cold" (possibly malignant). In a multinodular gland with predominant nodules, directional counting is also done. Whereas 23% of the physiologically hypoactive nodules have been found to be malignant, the hyperactive nodules are uniformly benign. These nodules may successfully be treated medically.

The Prognosis of Patients with Intermittent Claudication. W. B. Spaulding. Canad. M. A. J. **75**:105-111 (July 15) 1956 [Toronto, Canada].

One hundred one men and seven women with intermittent claudication were studied in an attempt to learn what facts are of aid in making a prognosis concerning the patient's life as well as the affected extremities. Thirteen patients died within three years of the onset of the disease and 22 died within five years, but not all the patients were followed up for this length of time. Patients in whom the onset of the disease occurred early in life lived longer, on the average, than patients with a later onset. Normotensive patients had a better prognosis regarding life than those with hypertension. The group with unilateral claudication had a somewhat lower mortality rate than the group with pain in both lower extremities. Manifestations of cardiovascular disease were common in the patients during their lifetime, and atherosclerosis played a striking role in causing death. The incidence of cardiovascular disease was higher in patients with hy-

pertension than in normotensive patients. Amputations were performed in 27 patients (25%). The first amputation was usually carried out within five years of the onset of intermittent claudication. Amputation was performed more often in patients with unilateral claudication than in those with bilateral claudication, but it was required less frequently in those with hypertension than in those with normal blood pressure because ischemic complications occurred less frequently in hypertensive than in normotensive legs.

Portal Hypertension Due to Chronic Occlusion of the Extrahepatic Portion of the Portal Vein: Its Relation to Ascites. A. H. Baggenstoss and E. E. Wollaeger. Am. J. Med. 21:16-25 (July) 1956 [New York].

From 213 autopsy patients with the anatomic diagnosis of occlusion of the portal vein the authors excluded all those with ascites in whom any coexistent lesion, such as concomitant cirrhosis of the liver, peritoneal carcinomatosis, chronic peritonitis, renal disease, congestive heart failure, obstruction of hepatic veins, Meigs' syndrome, myxedema, or obstruction of the inferior vena cava above the liver, which might by itself have been responsible for ascites, was found. This method of selection uncovered 15 cases of ancient thrombosis of the portal vein uncomplicated by any other condition that might cause ascites. In 10 of these cases no ascites was present; in 5 ascites was present and was of long standing. In addition to the pathological findings, the clinical findings and the course of the disease were studied in these 15 cases. In the group with portal obstruction without ascites there were five men and five women and their average age was 30 years. In the group of portal obstruction with ascites there were two men and three women and their average age was 45 years. Clinical and pathological evidence of portal hypertension was found in all 15 cases. Attempts to produce ascites in experimental animals by obstruction of the portal vein alone have for the most part been unsuccessful. Contrary to the results of these experiments, the authors' observations in five cases of chronic occlusion of the portal vein in which ascites could be attributed solely to this lesion emphasize the role of portal hypertension *per se* as an important contributing factor in the pathogenesis of ascites, even in the absence of hypertension of the intrahepatic portal system.

Comparison of the two groups of patients, those in whom ascites was present and those in whom it was absent, revealed that in the group without ascites the mean age was lower, the occurrence of better-developed accessory portal veins (hepatopetal circulation) was more frequent, and the degrees of enlargement of the spleen and of atrophy of the liver were less. Although no great significance can be ascribed to these differences because of the small number of cases in the two groups, these findings suggest that inadequate development of the hepatopetal collateral circulation may be a determining factor in the development of ascites in some cases of chronic occlusion of the portal vein.

Treatment of Addison's Disease. K. Emerson Jr. A.M.A. Arch. Int. Med. 98:100-105 (July) 1956 [Chicago].

When the diagnosis of adrenal insufficiency is made in a patient who is critically ill with the vascular collapse characteristic of an Addisonian crisis, a continuous intravenous infusion of from 2,000 to 3,000 ml. of 5% dextrose in isotonic sodium chloride solution containing 100 mg. of dihydrocorticosterone per liter should be started at once. The total volume of fluid must depend on the degree of shock and dehydration and the state of the cardiovascular system. The amount of hormone given should never be less than 200 mg. in the first 24 hours. Intravenous therapy should usually be continuous during the first 24 hours, because the patient may relapse into shock within 4 to 6 hours after its discontinuance unless he is supported by oral or intramuscular administration of hormone. Oral therapy is preferable to intramuscular because absorption is faster by the oral route and higher blood levels are obtained. Another 1,000 to 2,000 ml. of 5% dextrose in saline containing a total of 100 mg. of dihydrocorticosterone should be given on the second day over an 8-to-12-hour period. Frequent feedings with a bland high-carbohydrate diet may be started unless contraindicated by the condition precipitating the Addisonian crisis, such as a surgical operation. At least six hours before the end of this infusion, oral therapy with 25 mg. of cortisone every six hours should be begun. Most patients, by the third day, will be able to consume a normal diet and be maintained on cortisone given orally in doses of 25 mg. every six hours. This dose can be reduced subsequently by 25 mg. each day to the final maintenance level of 12.5 mg. twice daily by the end of a week.

When the diagnosis of Addison's disease has been established by the appropriate diagnostic procedures in a patient in whom the onset of symptoms has been gradual and who is not critically ill, oral therapy may be started at once according to the following regimen: 25 mg. of cortisone or 20 mg. of hydrocortisone is given on arising and again after 6 to 12 hours for one week or until distinct improvement in strength, appetite, and sense of well-being is observed. The dose is then reduced to 12.5 mg. of cortisone or 10 mg. of hydrocortisone given twice daily. The introduction of fludrocortisone, a potent hormone capable of supplying adequate salt retention in doses varying from 0.1 to 0.2 mg. per day, has simplified the management of patients with Addison's disease. Although it is necessary to continue the use of cortisone or hydrocortisone in combination with the fluorine-containing compound, it is becoming apparent that in some cases adequate maintenance can be achieved with only one-half of the previously indicated quantity of the glucocorticoids, namely, 12.5 mg. of cortisone or 10 mg. of hydrocortisone once daily. In a certain proportion of patients, especially those with relatively long-standing adrenal insufficiency, a period of several months may elapse before the full beneficial effect of replacement therapy will become evident. Eventually, however, by the proper adjustment of dosage, the patients with Addison's disease can be restored to normal health and activity.

Cortisone Test in Adrenal Hyperplasia and Adrenal Tumor. S. Wais. Medicina 16:1-10 (Feb.) 1956 (In Spanish) [Buenos Aires, Argentina].

The cortisone test for differentiating adrenal hyperplasia from adrenal tumor was performed in eight women ranging in age from 17 to 46 years. The group included three patients with bilateral adrenal hyperplasia, three with Cushing's syndrome, and two normal women. The Cushing's syndrome was due to bilateral adrenal hyperplasia in one patient and to unilateral adrenal tumor (adenoma and carcinoma respectively) in two patients. The test was made by Jailer's technique, which involves determination of the urinary 17-ketosteroids before and during administration of cortisone intramuscularly in daily doses of 200 mg. for three or four consecutive days up to a total of 600 or 800 mg. The urinary 17-ketosteroids greatly diminished by the end of the treatment in all four patients with bilateral adrenal hyperplasia, whereas the figures did not change after the treatment in the two patients with adrenal tumors. In the patient with carcinoma the urinary 17-ketosteroids increased during the administration of the hormone. In the two normal women, the urinary 17-ketosteroids diminished after administration of the hormone. The test is reliable for differentiating adrenal hyperplasia from adrenal tumor.

Smallpox in France: Recent Epidemiological Data. R. Crosnier. Semaine hôp. Paris 32:2198-2203 (June 22) 1956 (In French) [Paris, France].

One of the epidemics of smallpox in France during the period 1954-1955 occurred in the Morbihan department. There were 73 cases and 16 deaths. Special reference is made to the pulmonary forms presenting noninfectious labile infiltrate and to the pure febrile forms. Mass inoculation has occasioned skin conditions similar to those encountered during the epidemic at Marseilles in 1952. There is a close relation between vaccinal ectodermotrope virus and other equally ectodermic viruses. If dermatosis appears, it will occur generally between the 8th and the 13th day at the time of the maturity or at the beginning of the decline of the vaccinal lesion. After 15 days the complication will not appear.

The increasing role of allergy is discussed. Jennerian vaccination can reveal allergic processes that are homologous or foreign, unsuspected or latent, and confer on certain substances an acci-

dental skin tropism in making them true reactogens. Their clinical consequences are frequently dependent on the character and degree of the vaccinal reaction. Whatever the criticism, Jennerian vaccination never proved ineffective in the contaminated area. Antivariolic vaccination has been regarded as a factor in the genesis of acute coronary thrombosis (eight cases with five deaths between the 7th and the 14th day). Contraindications to antismallpox vaccination are very limited, although some of them are absolute and permanent, for example, leukemias and diabetic states. In many circumstances allergy in a large and general sense plays an undeniable part in contraindication. In addition, although observed clinical conditions have until now seemed to result only from the infectious disease process, at present the allergic phenomenon must also be considered in the course of the development of certain smallpoxes. A late vaccination that is given after smallpox contagion and is therefore not inhibitive of the disease may produce allergic phenomena in certain cases. These phenomena should be investigated and dissociated from the true disease state. Contraindications must not be carelessly multiplied. There are certain cases where precautions and preventive measures are necessary with regard to Jennerian vaccination. However, in spite of possible but rare untoward side-effects or late effects, Jennerian vaccination remains indisputably the one irreplaceable and efficient prophylactic weapon against smallpox. Performance of mass vaccinations and revaccinations should be carried out without delay, not only locally but also in surrounding areas, in the event of an outbreak. Every certain or possible contact demands immediate vaccination.

Clinical Diseases of Adults Associated with Sporadic Infections by APC Viruses. E. Jawetz, L. Hanna, S. J. Kimura and P. Thygeson. A.M.A. Arch. Int. Med. **98:** 71-79 (July) 1956 [Chicago].

Adenoidal-pharyngeal-conjunctival (APC) viruses are widely accepted at present as important causative agents of epidemic respiratory disease in military recruits and in children. An attempt was made by the authors to throw light on the role of these pathogenic agents in the causation of sporadic illness in adults. Five cases are described in men between the ages of 26 and 50 years, illustrating infection with adenoidal-pharyngeal-conjunctival viruses of types 2, 3, 6, 7, and 8. The illnesses ranged from simple mononuclear conjunctivitis without fever or respiratory symptoms to a severe influenza-like systemic disease, necessitating prolonged hospitalization. Types 2, 3, 6, and 8 of the APC viruses were isolated from the eyes in 9 of 22 patients whose clinical picture strongly suggested causation by these pathogenic agents. Involvement of the eye was observed by the authors in most of the proved sporadic APC virus infections in adults. In some the eye was the only site of manifest viral activity; in others it was associated with systemic or respiratory symptoms. The constancy of eye involvement suggests the role of the eye as a probable portal of entry and a site of major manifestations of APC virus infection.

The Use of Corticosteroids in Combination with Isonicotinic Acid Hydrazide in the Treatment of Advanced Bilateral Progressive Cavitary Pulmonary Tuberculosis. A. E. Handley. South African M. J. **30:**605-608 (June 30) 1956 [Cape Town].

This is a preliminary report on a three months' trial of prednisone (Meticorten) and isoniazid (isonicotinic acid hydrazide) in the treatment of 23 Bantu females varying in age from 12 to 45 years. All had bilateral, advanced, progressive pulmonary tuberculosis with cavitation and with gross secondary pulmonary sepsis; they had had at least six months' hospital treatment (some had had previous admissions dating back to 3 or 6 years); their conditions were deteriorating under routine treatment; they were gravely ill with prognoses varying from poor to extremely bad; and they were obviously unsuitable for any form of operative procedure. Isoniazid was given in daily doses of 15 mg. per kilogram of body weight, as the only antituberculous drug. Antibiotics and sulfonamides were given in accordance with the response of secondary organisms cultured from the sputums. Complications such as amebiasis were treated as indicated at weekly examinations. The hospital diet was supplemented with extra protein in the form of a broth of protein hydrolysate, vitamin-B complex concentrate, and vitamins C and D. Hemopoietic substances and blood transfusions were given as indicated by blood investigations. Up to this point, treatment consisted of what might have been given under routine hospital procedure.

Prednisone (Meticorten) was given in daily quantities of 15 mg., subdivided in three doses, regardless of the weight of the patient. At the end of three months this dose was gradually reduced, while corticotropin was administered in increasing dosage as an adrenocortical stimulant. No patient died during this therapeutic trial, although a fatal outcome would have been anticipated in the majority of cases of this type. All patients exhibited marked clinical improvement. All but one showed satisfactory weight gains. On independent radiological assessment no patient showed further deterioration and five actually showed slight improvement; however, tubercle bacilli were always present in the sputum.

Oral Treatment of Diabetes Mellitus with Invenol: Indications and Contraindications; Insulin-Resistant and Invenol-Resistant Diabetes: Factors Causing a Renal Effect. J. Blöch and A. Lenhardt. Wien. med. Wchnschr. **106:**394-398 (July 7) 1956 (In German) [Vienna, Austria].

Highly satisfactory results were obtained with Invenol, a proprietary preparation of carbutamide, in 400 patients with diabetes mellitus. Treatment was started with a daily dose of 4 or 3 gm. After a few days the dose of the drug was reduced to 2, 1, or 0.5 gm., and that was used as the maintenance dose. Undesirable side-effects consisted of anorexia, stomach-ache, and heart-burn in 2 patients and of a toxic morbilliform or urticarious rash in 10. The rash subsided within a few days after withdrawal of the drug. The drug did not cause any damage to the liver, kidneys, nervous system, or morphological elements of the blood, particularly the leukocytes.

Carbutamide therapy is indicated in patients with diabetes mellitus who are sthenic in type, with a tendency to obesity, and of middle or advanced age, i. e., in patients with "diabetes with insulin resistance." Carbutamide therapy is contraindicated in hyposthenic patients with "insulin-deficiency diabetes," i. e., diabetes with resistance to carbutamide. It is contraindicated in children and adolescents with diabetes mellitus, in pregnant women at least during the last months of pregnancy, in patients with intercurrent disease, and in those with acidosis. Surgical intervention or the preoperative period are contraindications to carbutamide therapy. From one-third to one-half of the patients with diabetes mellitus may be treated successfully with carbutamide. Insulin remains fully effective after the withdrawal of carbutamide. The positive effect of carbutamide can be reproduced at any time. Carbutamide is not a substitute for insulin, but it either stimulates the beta cells or increases, by enzymatic action, the effect of the endogenously produced insulin. Two observations were made that suggest that the mechanism of action of carbutamide differs from that of insulin. Old insulin frequently causes a rapid decrease in the excreted amount of urine, whereas carbutamide causes polyuria. Insulin causes a simultaneous decrease in the blood sugar level and in the amount of sugar excreted in the urine. Glycemia may be restored to normal by carbutamide, but increased glycosuria may persist. It is suggested that carbutamide exerts an influence on the tubular reabsorption of water and sodium and perhaps also on that of sugar.

The Problem of Chronic Liver Disease in Young Women. A. G. Bearn, H. G. Kunkel and R. J. Slater. Am. J. Med. **21:**3-15 (July) 1956 [New York].

This report deals with 26 young adult patients with cirrhosis of the liver whose symptoms and signs differed from those of patients with the more comon type of cirrhosis. The predominance of women in this group was striking, since only 3 of the 26 patients were men. The average age of the patients at the onset of the disease was 15 years. Delayed menstruation or amenorrhea before or coincident with the onset of symptoms related to liver disease occurred in 15 of the 23 women. In four patients acne, hirsutism, pigmented striae, obesity, and moon facies were also noted before the recognition of liver disease. In some patients transient rashes similar to those seen in erythema multiforme were observed early in the course of the disease. The well-nourished and relatively healthy appearance of these patients be-

lied the seriousness of their disease. As the disease progressed, the classic signs of hepatic cirrhosis became increasingly apparent. The spleen was usually considerably enlarged and was frequently palpable at the earliest recognizable stage of the disease. Spider angiomas and liver palms developed in most of the patients. Clinical ascites, in sharp contrast to the findings in many patients with Laennec's cirrhosis, was relatively uncommon in these patients in the early stages of the disease. In 10 patients obscure febrile episodes sometimes associated with respiratory or cardiac symptoms occurred at some time in the course of the disease. Numerous blood cultures were performed in an attempt to isolate a causative agent, but in none of the patients was a positive blood culture obtained. Eleven patients (42%) complained of joint pains of varying degree. These symptoms usually occurred early in the course of the illness and in some patients were accompanied by an acute non bacterial febrile attack associated with a temporary exacerbation of the liver disease.

Twelve patients died as a direct result of the disease process, of either esophageal hemorrhage or progressive hepatic coma. The average duration of the disease in these patients was about seven years. The mean duration of the disease in those still living is five and a half years. Striking improvement followed the use of cortisone in some patients. Continued use of small doses of cortisone may be of some value but there is as yet no conclusive evidence that cortisone has modified the disease process or that it will alter the eventual outcome. Laboratory studies in the acute stages of the disease usually revealed an extremely high serum gamma globulin level and an increase in the plasma cells of the liver. The possibility that specific endocrine influences, present in young women, may modify the usual course of infectious hepatitis has been discussed. In most of the patients the causation of the disease process was uncertain.

SURGERY

Complications of First Rib Fracture, Including One Case Each of Tracheoesophageal Fistula and Aortic Arch Aneurysm. T. W. Holmes Jr. and R. E. Netterville. J. Thoracic Surg. 32:74-91 (July) 1956 [St. Louis].

Seventeen (10%) of 170 patients who were hospitalized between Jan. 1, 1947, and Dec. 31, 1954, with a diagnosis of fractured ribs, had fractures of one or both first ribs, isolated or in addition to other rib fractures. All of these fractures, with the exception of those in one patient, were produced by closed chest trauma, in most cases by sudden deceleration in an automobile accident in which the chest sharply struck the steering wheel. Severe mediastinal complications occurred in 2 of the 17 patients with first-rib fracture; in one patient an esophageal diverticulum with tracheoesophageal fistula was diagnosed six months after the injury, and in the other patient a fusiform aneurysm of the aortic arch was diagnosed more than two years after the injury. The tracheoesophageal fistula was successfully repaired by direct division and suture. The aneurysm, which was entirely asymptomatic, was covered with reactive polyethylene and responded well to this conservative surgical treatment. Other complications in the patients with first-rib fracture included injury to the brachial plexus and stellate ganglion and an unusual obstruction of both subclavian veins from the pressure of excessive callus about the healing bilateral fractures. Remaining complications in this group of patients were the common sequelae of pleural puncture by the rib fragments.

As a result of their experience and a survey of the world literature concerning first-rib fractures, traumatic tracheoesophageal fistula, and traumatic aneurysm, the authors state that trauma sufficient to produce fracture of a first rib by indirect force is capable of causing injury to mediastinal soft parts. Lesions of lesser magnitude than complete disruption of the tracheobronchial tree or great vessels may be considerably delayed in development or in producing diagnostic symptoms or signs. In patients with closed thoracic injuries, especially those produced by high-speed automotive accidents, one must search carefully for evidence of first-rib fracture, which may be easily overlooked before callus formation begins. Patients with such fractures without early manifestations of mediastinal lesions must be thoroughly examined at frequent intervals for at least two years after the injury. Each examination should include a roentgenogram of the chest. Widening of the superior mediastinal shadow in the vicinity of the aortic arch following chest injury should be considered a sign of possible incomplete rupture of the aorta or other great vessel from which an aneurysm may develop.

The Physiologic Effects of Fibrothorax and the Functional Results of Surgical Treatment. A. A. Siebens, C. F. Storey, M. M. Newman, and others. J. Thoracic Surg. 32:53-73 (July) 1956 [St. Louis].

Eleven patients, 10 of whom were men less than 35 years old, required pleural decortication of either a tuberculous or a nontuberculous pleural peel. The right side of the chest was the site of the disorder in five patients and the left side in six. The duration of the disorder varied from 2 months to 13 years. The patients were evaluated from a respiratory point of view both before and after the operation. The tests performed pertained to unilateral and bilateral ventilation and total lung volumes, intrapulmonary mixing of respiratory gases, ventilation-perfusion relationships, and relative dimensions of the diffusing surface (maximum diffusing capacity).

The preoperative deficit usually consisted of impaired ventilation, diminished lung volumes, and a reduction in the dimensions of the alveolar capillary bed. Defects in the mixing of gases within the lung and in the relationship between ventilation and perfusion were uncommon. Pleural decortication was usually followed by improved ventilation, increased lung volumes, and restoration of alveolar-capillary units. Among the most constant effects of the operation in these patients was an increase in residual volume, a change that could be attributed to the removal of a noncommunicating intrathoracic mass and to the release of retracted parietes. Associated roentgenographic findings were the elimination of density between the lungs and thoracic wall and the widening of the intercostal spaces, which was frequently seen postoperatively. This increase in residual volume, either absolute or relative to the total lung capacity, should not be identified with "overdistention" and construed as detrimental to function. The functional residual capacity was also commonly augmented by the operation, and the reasons for this increase paralleled those cited for the changes in residual volume. Comparison of tuberculous and nontuberculous groups indicated no striking differences with respect to the patients' postoperative respiratory status. Duration of disease, parenchymal involvement, postoperative complications, and the degree of preoperative functional impairment were factors contributing to the extent of recovery. Protracted disease did not preclude improvement.

Despite postoperative improvement, no patient was fully restored to normal by operation. The period of convalescence before the postoperative study was three months or less in most of the patients. This short postoperative interval accounted in part for the limited recovery. No gross deficit occurred as the direct result of surgery. Consistently with the essentially mechanical nature of the impairment imposed on the lungs by pleural envelopment, the physiological abnormalities produced were reversible to varying degrees by surgical removal of the confining structures.

Surgery of Eventration of the Diaphragm. E. F. Chin and R. B. Lynn. J. Thoracic Surg. 32:6-14 (July) 1956 [St. Louis].

Eventration of the diaphragm, a congenital, abnormally high position of the intact diaphragm, was observed in 18 male and 19 female patients between the ages of 13 and 72 years. Five of the 38 patients were treated successfully by surgery. Four of these patients had symptoms, including epigastric pain, flatulence, belching, and severe melena, that required surgical treatment. The fifth patient, a 13-year-old boy, had no symptoms, but it was felt that the extensive defect warranted repair. A careful dissection around the chest wall and the pericardium is imperative, mobilizing the muscular portion of the diaphragm to its fullest extent. This muscular portion is often well hidden and appears almost to be covered by its own membrane. Once it is fully mobilized, the affected portion of the diaphragm can be resected and muscle-to-muscle suture performed. In none of the patients was it difficult to obtain muscular apposition, and postoperative roentgenologic examination showed an intact diaphragm with limited but normal movement on respiration. No reinforcement, such as tantalum mesh or fascia lata grafts, was necessary.

The Nonoperative Treatment of Traumatic Chylothorax. J. V. Maloney Pr. and F. C. Spencer. Surgery 40:121-128 (July) 1956 [St. Louis].

The increasing number and scope of intrathoracic surgical procedures has been accompanied by a rise in the incidence of chylothorax, and the mortality rate of this surgical complication has been found to be as high as 50%, although this rate has shown a progressive decrease during the last 10 years. The trend toward the early surgical treatment of chylothorax by ligation of the thoracic duct is now well established. The purpose of the present discussion is to temper the current enthusiasm for early operative intervention. Thirteen patients with chylothorax were treated without morbidity or mortality. Eleven of these responded to the simple expedient of multiple thoracenteses. Two patients were subjected to a second operation, but on the basis of their present knowledge the authors feel that in these patients closed catheter drainage could have been tried before operation. They are convinced that persistence with nonoperative treatment by thoracenteses or closed catheter drainage will be rewarded with a high degree of success.

Esophageal Dystonia. R. H. Schug. West. J. Surg. 64:391-393 (July) 1956 [Portland, Ore.].

Esophageal dystonia is the author's choice of the four terms that have been applied to a noninflammatory, non-neoplastic constriction of the lower esophagus. The other three terms are cardiospasm, achalasia, or megaesophagus, the latter term referring to the enlarged esophagus proximal to the constriction. The condition is due to a localized defect in autonomic innervation. Several medical and surgical treatments have given poor long-term results. The author describes a surgical method that neither produces a sliding hernia nor damages the diaphragmatic crura. A transthoracic approach is used, and, if a sling type of hernia exists, it can be visualized and repaired.

After the chest is opened through the bed of the eighth rib, the phrenic nerve is anesthetized and a radial incision is made in the dome of the diaphragm at a distance from the esophageal hiatus, care being taken not to interfere with the sphincter action of this hiatus. Through the opening in the diaphragm a high gastrotomy is carried out, and the index finger is inserted through it into the esophagus. With the finger in this position and under direct vision, the pleura over the esophagus is incised and an anterior, extramucosal myotomy is carried out. The incision is made long enough to open the entire constricted area, but does not extend more than 2 cm. beyond it at either end. The esophagus is not dissected from its bed and is disturbed as little as possible. After the myotomy, a Levin tube previously introduced into the dilated portion of the esophagus is threaded through into the stomach. The tube may be removed and fluids and food may be given as early as 48 hours after the operation. Two illustrative case histories are presented. An extramucosal esophageal myotomy is a safe and simple method that will produce cure. The procedure minimizes the possibility of postoperative regurgitation. Severe esophageal dystonia requires prompt surgical treatment.

Pulmonary Resection as an Adjunct in the Treatment of Pulmonary Tuberculosis. J. W. Gale, H. Dickie, J. Rankin and A. R. Curreri. Am. Rev. Tuberc. 74:29-41 (July) 1956 [New York].

The authors present observations on 1,165 patients in whom resection was carried out as an adjunct to the treatment of pulmonary tuberculosis during the 10-year period ending in May, 1954. There was a sharp increase in resections after 1950, because under the influence of long-term chemotherapy surgical resection became possible at a better than reasonable cost in terms of operative mortality and postoperative complications. The general goal of drug therapy was the attainment of maximal resolution of reversible disease and the closure or eradication of open lesions. Persistent necrotic lesions, which often harbored viable bacilli, were then resected. In this way it was possible to restrict the extent of resections and preserve pulmonary tissue. The optimal time for surgical intervention varied considerably, depending on the extent and severity of the disease, the age of the patient, and the presence of complications such as endobronchitis. On the average, a patient received antimicrobial therapy for from 9 to 15 months prior to resection. Bronchoscopy was performed several days before resection in nearly all patients. If any evidence of endobronchitis was present, surgical intervention was delayed. In some instances the addition of oxytetracycline to the antimicrobial therapy cleared the minor endobronchitis. The greatest therapeutic challenge, however, was the patient with persistent cavitation and endobronchitis whose tubercle bacilli had lost susceptibility to streptomycin and isoniazid. Pulmonary resection in these patients was hazardous because of the greatly increased risk of bronchopleural fistula. Prevention of the development of resistance to drugs is of primary importance in these patients.

At present the tendency is to resect a cavitary lesion at an earlier period rather than to wait for reversal of infectiousness and cavitary closure to occur, if this has not been accomplished after a four-to-six-month period of treatment. If either streptomycin or isoniazid has not been used, it is added to the drug regimen. If surgery is regarded as feasible, the resection is planned within the four-to-six-week interval after the addition of the streptomycin or the isoniazid. However, if, in spite of roentgenographic evidence of residual cavitation, the sputum no longer contains tubercle bacilli on microscopy or culture, the period of preoperative chemotherapy may be extended if the extent of removable pulmonary tissue can thus be significantly decreased. The authors were able to obtain information on 1,115 patients who were followed for from 1 to 10 years. The operative mortality was 3%. An additional 3% of the patients have died in the intervening years from various causes, including active pulmonary tuberculosis. Two per cent of the patients still have active tuberculosis, but 1,015 (91%) of the 1,115 who could be traced are clinically well and are classified as having inactive tuberculosis.

Evaluation of Vagotomy and Pyloroplasty in the Treatment of Duodenal Ulcer. H. E. Dorton. J. Kentucky M. A. 54:602-609 (July) 1956 [Louisville, Ky.].

Dorton reports on vagotomy combined with a drainage procedure in 151 patients with duodenal ulcer. Early in their use of vagotomy they found that symptoms of mechanical pyloric obstruction would sometimes develop and be troublesome. A drainage procedure was added in order to overcome this difficulty. Pyloroplasty was done, because it would allow confirmation of the diagnosis, removal of the scarred area, and restoration of the anatomy to a more natural state.

At operation the diagnosis is first confirmed by inspection of the region or, if necessary, by opening of the pylorus and of the first part of the duodenum. Then subphrenic vagotomy is carried out, great care being taken that no branches of the nerve are overlooked. A complete vagotomy is more readily carried out if the esophagus is drawn well down into the abdomen so that the two main trunks of the nerve are reached rather than the arborization further down. Then attention is given to the drainage problem. In all but five of the 151 patients it was possible to perform a pyloroplasty. The simplest type, that of Judd or Mikulicz, was used 123 times. It consists of a linear incision of the pyloroduodenal junction so that two fingers can be inserted into the duodenum and up into the stomach. The ulcerated area is trimmed away and the opening is closed transversely. A neat closure is almost always followed by a smooth convalescence and a good result. Rough handling or inversion of too much tissue is likely to interfere with drainage and jeopardize the result. When the ulcer is located on the posterior-superior or the posterior-inferior duodenal wall, the area is wedged out. The resulting V-shaped defect is closed side-to-side and the remainder of the closure is the same as for simple anterior-pyloroplasty. This has been used 14 times in this group. These simple procedures are inadequate when the duodenum is greatly distorted or the ulcer is deeply embedded in the pancreas. In these patients, the author cuts across the duodenum just distal to the area and across the pylorus just proximal to the sphincter and discards the intervening unhealthy tissue. The stomach is then joined to the open end of the duodenum in a simple end-to-end anastomosis as in the Billroth 1 operation. This procedure was used seven times in this series.

A short-loop posterior gastroenterostomy was necessary in five of the patients. There were two deaths in the 151 patients; satisfactory results were obtained in 91% of the cases. The average hospital stay after surgery was a little over eight days. The effect of the procedure on the patient's weight was very encouraging. The author concludes that vagotomy and pyloroplasty is a satisfactory method for treating nearly all types of complicated duodenal ulcer. Bleeding ulcer is amenable to the same treatment provided the ulcer is removed. The ability to eliminate side-effects appeared to be directly proportional to the ability to restore the pyloroduodenal outlet to as nearly normal size and contour as possible. A patient who has obtained a good result usually remains well.

Colon Polyps and Unexplained Rectal Bleeding. G. C. Tyler. West. J. Surg. 64:374-376 (July) 1956 [Portland, Ore.].

In the absence of an obvious carcinoma, bleeding from the rectum that is not explained by anorectal lesions is frequently due to polyps of the colon and their sequels. Approximately 10% of patients over the age of 40 have adenomas or polyps of the colon. Bleeding occurs when these lesions reach a diameter of about one-half inch, so that the passage of feces causes ulceration. The clue therefore is bleeding. Diagnostic routine involves, in the order named, rectal examination and sigmoidoscopy; barium enema; air-contrast barium enema; and exploration of the abdomen and colposcopy. Forty-one cases are renewed. The presence of a polyp was verified by laparotomy in all 41 patients. The author stresses the fact that if in the presence of bleeding from the rectum a lesion cannot be found by repeated sigmoidoscopy and if repeated x-ray studies are inconclusive, then laparotomy and direct sigmoidoscopic visualization of the colon are imperative. Operative mortality and morbidity are so low as to be almost never a contraindication to laparotomy.

The Ulcerogenic Tumor of the Pancreas. E. H. Ellison. Surgery 40:147-170 (July) 1956 [St. Louis].

Ellison is concerned with a new clinical entity consisting of a fulminating and frequently fatal peptic ulceration associated with a non-insulin-producing islet cell tumor of the pancreas. A review of the clinical records and autopsy protocols of all patients admitted to the Ohio State University Medical Center during the past 10 years with the diagnosis of peptic ulceration and/or pancreatic tumor disclosed five patients with this disorder. These five cases bring the total of reported "ulcerogenic tumors" of the pancreatic islets to 24. Although 19 of the 24 islet adenomas were malignant, the rate of growth was slow and peptic ulceration remained the predominant manifestation in nearly all of the patients. Only 11 of the 19 malignant tumors had spread beyond the confines of the pancreas.

This new clinical entity is characterized by excessive gastric secretion and rapidly progressive, atypically located ulcers recurring despite adequate medical or surgical therapy. The associated tumor remained unrecognized until autopsy in nine patients, who underwent 23 operations for 35 primary and recurrent marginal ulcerations and who died of ulcer with an average survival time of 17 months. The tumor was removed at operation in 11 patients with complicated ulcer disease, and of these, 5 are living. Three patients died of ulcer, and in each instance overlooked islet tumors were found in the pancreatic remnant. The remaining three patients succumbed to recurrent tumor. The average survival time in the six fatal cases was 6.6 years, which represents a considerable improvement over results obtained in the patients in whom the pancreatic tumor was overlooked. Furthermore, the improved results indicate the importance of the tumors in the pathogenesis of this invariably fatal ulcer disease.

Documented observations of the return of gastric secretions to normal levels after resection of a non-insulin-producing islet cell tumor of the pancreas in a patient with hypersecretion and recurrent marginal ulcerations suggest that a hormonal or chemical factor arising in the pancreatic tumor is capable of stimulating the gastric glands to secrete and may be the causative agent of the ulcer disease. Until such time as better methods of diagnosis are available, it seems reasonable to suggest that a careful search of the pancreas should be made in all patients operated on for peptic ulcer. This is particularly important in patients with atypically located primary ulcer or those operated on for recurrent marginal ulceration. The surgical attack should include removal of the tumor, combined with some standard ulcer procedure designed to protect the patient in the event of recurrent or residual tumor. Finally, the difficulties encountered in palpating a small pancreatic adenoma suggest that resection of the body and tail of the pancreas may be advisable before subjecting a patient to total gastrectomy as a final heroic method of controlling the acid factor.

Carcinoid (Argentaffin) Tumors of the Gastrointestinal Tract. W. G. Diffenbaugh and R. E. Anderson. A. M. A. Arch. Surg. 73:21-37 (July) 1956 [Chicago].

Diffenbaugh and Anderson review the records of all patients with carcinoid tumors found in the files of St. Luke's Hospital, Chicago. Langhans described a carcinoid tumor as early as 1867, although he did not recognize it as such. Lubarsch in 1882 first used the term "little carcinomas," and Oberndorfer designated these tumors as "carcinoids" in 1907. The term "argentaffin" was first applied to them by Gosset and Masson, who found that cells within these tumors took a silver stain. It is now generally accepted that carcinoid tumors arise from the Kulchitsky cells of the crypts of Lieberkühn of the gastrointestinal tract. Carcinoid tumors have been reported as occurring in the stomach, gallbladder, duodenum, small intestine, Meckel's diverticulum, appendix, ileocecal valve, cecum, colon, rectum, and in the gastrointestinal components of teratomas of the ovary. Nearly 75% of the 51 carcinoid tumors in the files of St. Luke's Hospital were appendiceal in location.

Grossly, carcinoid tumors are light yellow in color, probably because of their high lipoid content. They are usually antimesenteric and submucosal in location in the intestinal wall. The typical cell is a small epithelial cell with an oval or round nucleus that has a well-defined nuclear membrane and a fine stippling of chromatin. The cytoplasm is palely acidophilic, small in amount, vacuolated or granular. The cells are in columns, nests, coils, or masses. Tumor cells in the metastatic foci may look benign by the usual histological criteria of malignancy. Frequently the cells in the metastatic deposit may take on an entirely different histological arrangement from that seen in the primary tumor. The carcinoids of the small intestine may manifest themselves by an acute obstruction due to intussusception of a polypoid tumor. This obstructive feature, as well as various other aspects of carcinoids of the small intestine, such as their multiplicity and their association with liver metastases, are illustrated on the basis of case histories. Liver metastases from carcinoid tumors of the small intestine may be associated with cyanosis, peripheral vasomotor symptoms, pulmonic stenosis, and tricuspid regurgitation without septal defects. The vascular lesions are presumably secondary to the prolonged action of serotonin, secreted by the tumor tissue. That carcinoid tumors may be functioning neurocrine tumors related to pheochromocytomas has been suggested in several reports.

Carcinoid tumors may appear anywhere along the gastrointestinal tract from the stomach to the anus. Histologically, the appendiceal carcinoids show frequent invasion of the muscle and serosal layers of the appendix, even though evidence of lymph-node metastases is infrequent. This type of tumor, wherever located, is malignant. The incidence of metastases of these tumors in various areas of the gastrointestinal tract usually parallels the stage in time at which the tumor is detected.

Treatment of Arteriosclerotic Occlusive Disease in 101 Lower Extremities by Arterial Homografts. E. S. Crawford, O. Creech Jr., D. A. Cooley and M. E. De Bakey. South. M. J. 49:665-670 (July) 1956 [Birmingham, Ala.].

Results from the conventional surgical therapy of arterial insufficiency in the lower extremities (sympathectomy and amputation) have been disappointing. In spite of sympathectomy, approximately one-third of these extremities ultimately required amputation. Fortunately, many arteriosclerotic occlusive lesions are segmental in character and an unobstructed distal segment is often satisfactory for anastomosis, permitting effective treatment with restoration of circulation distally. This paper is concerned with the use of lyophilized arterial homografts in the

treatment of 101 extremities with arteriosclerotic occlusive lesions located distal to the level of the aortic bifurcation. The primary objective of operation is to restore normal pulsatile blood flow into the distal arterial bed and simultaneously to minimize the tendency to recurrence of the occlusive process and to impose minimal risk on the existing circulation in the event of failure. When arterial homografts were first used by the authors, the short, discrete, occlusive segment was completely excised and replaced by a homograft sutured end-to-end to the host artery; this was done on 26 extremities. More recently, however, no attempt has been made to excise the involved vessel, the occluded segment being by-passed by an arterial homograft sutured end-to-side into the artery proximal and distal to the block, as suggested by Kunlin. Thus, in 75 cases the by-pass procedure was used.

Restoration of circulation distal to the occlusion, as determined by arteriography or by the presence of pulses, was accomplished in 92 of the 101 extremities treated. Among 12 patients with femoral occlusion treated by excision and end-to-end grafting there were 3 unsuccessful results, but the same procedure was performed on 14 patients with iliac obstruction without a failure. Failures followed the by-pass procedure in 3 of 29 patients with femoral occlusion and in 3 of 46 with iliac occlusion. In general, failure occurred in borderline cases in which the distal segment was sclerotic and out-flow from the graft was poor. It is estimated that amputation was prevented in 18 cases.

Thyroidectomy and the Recurrent Laryngeal Nerves. A. D. Roy, R. H. Gardiner and W. M. Niblock. Lancet 1:988-990 (June 23) 1956 [London, England].

To ascertain the frequency, cause, and results of damage to the recurrent nerves during operations on the thyroid, Roy and associates examined the records of 300 patients operated on for nonmalignant conditions of the thyroid. All 40 patients showing damage to the recurrent nerve were followed up for at least a year. In 22 patients the right recurrent nerve was damaged, in 17 the left nerve, and in one patient both nerves were damaged. Complete recovery resulted in 18 of the patients, in 6 of whom the initial lesion was partial, manifesting itself as sluggishness and weakness in adduction of the vocal cord. Only two of these patients noticed any change in their voices. In 11 patients there was initially complete paralysis of a cord in the paramedian position midway between adduction and abduction, and in one patient the paralysis was partial within six days of operation and complete a month later. Movement of the vocal cord was not restored in 22 of the patients, including the one with bilateral lesions.

As regards the cause of damage to the recurrent nerves, in 19 patients difficulties were met with at operation. Emphasis is placed on the danger to the nerves at a low level in the neck in the presence of lower-lobe adenomas and in retrosternal prolongations. The nerves are also highly vulnerable where they are crossed by, or mingle with, the branches of the inferior thyroid artery. No operative difficulty was noted, and yet one of the nerves was damaged in 21 of the 40 patients. In 14 of these recovery resulted; presumably, the nerve was either stretched or caught in a hemostat in these patients. The prognosis of damage to the recurrent nerve is good. The recovery rate is high, and in patients in whom the nerve does not heal, compensation by the other vocal cord is usually good and functional recovery rapid and often complete. An accurate estimate of the frequency or extent of damage to the recurrent laryngeal nerves can only be obtained if the vocal cords are examined both preoperatively and postoperatively.

Late Results of Resections for Tuberculosis of the Upper Lobe. E. Hoffman. Thorax 11:160-162 (June) 1956 [London, England].

Hoffman reviewed the results of 100 resections for pulmonary tuberculosis of the upper lobe from one to six years after operation. The radiological appearances, sputum-conversion rate, complications, respiratory function, and working capacity were investigated. Serious postoperative complications (bronchopleural fistula, spread of disease) occur mainly in the first 12 months after the operation. There were no deaths in the late follow-up period. The majority of patients showed no clinical evidence of impaired respiratory function, and a large number were able to return to a normal working life. Primary resection of upper lobes was occasionally followed by poor results. This was the case in patients with large apical cavities and bilateral fibrocaseous disease, particularly when disease had at some time been present in the lower parts of the lung. Thoracoplasty still remains the procedure of choice for these patients. The reason for the decline in the popularity of this operation in some centers is the respiratory inefficiency that follows an extensive thoracoplasty. With present-day chemotherapy, the removal of more than five ribs should rarely be necessary. In extensive unilateral disease where the volume of the residual lung would not be sufficient to fill the space, thoracoplasty should be done as well as resection. This may be done either as a combined procedure or with the thoracoplasty as a preliminary operation. Resection has proved to be a satisfactory operation (1) in residual caseous foci, (2) in chronic fibrocaseous disease of segmental or lobar distribution, particularly if some degree of atelectasis is present, and (3) when thoracoplasty has failed.

The Surgical Treatment of Esophageal Stricture. L. D. MacLean and O. H. Wangensteen. Surg. Gynec. & Obst. 103:5-14 (July) 1956 [Chicago].

Eighteen patients with esophageal stricture have been treated by a surgical procedure designed to decrease acid-peptic irritation of the lower esophagus. Fifteen of them underwent subtotal gastrectomy, and in three hiatal-hernia repair accompanied by a Heineke-Mikulicz pyloroplasty was performed. In all 18 patients, complete disappearance (13 patients) or substantial improvement (5 patients) in dysphagia occurred. The period of observation after operation ranged from 4 months to 16 years. Gastric resection was carried out in one patient with an extensive corrosive stricture of the esophagus, with but slight improvement. An accompanying gastric or duodenal ulcer was observed in six patients; both duodenal ulcer and hiatal hernia were present in seven patients; both duodenal ulcer and hiatal hernia in one patient; and in four patients no concomitant anatomic abnormality was detected. Reestablishment of a fairly normal esophagogram after gastric resection was observed in even the most deformed and strictured esophagi in the follow-up roentgenograms, which were taken over a period of months. The esophageal lumen size, estimated by the size of the dilator that traverses the strictured area, increased markedly in the immediate and early postoperative period. Preliminary microscopic studies suggest that the depth of the esophageal lesion in acid-peptic esophageal stricture involves primarily the superficial layers of the esophageal wall (mucosa and submucosa) as contrasted with the stricture that results from the ingestion of corrosive caustic agents, in which the entire esophageal wall becomes involved in the fibrotic process. Gastric-acid production frequently is elevated in patients with esophageal stricture. Esophageal resection with intrathoracic or cervical esophagogastrostomy is recommended for lye or concentrated acid stricture. Two patients who were incapacitated and without lasting benefit from dilations have been restored to full health after resection of the esophageal stricture.

Carcinoma Associated with Ulcerative Colitis. R. H. Thorlakson. Surg. Gynec. & Obst. 103:41-50 (July) 1956 [Chicago].

Twelve cases of carcinoma of the colon and rectum found in 182 consecutive colectomies performed for ulcerative colitis at St. Mark's Hospital in London, England, were reported. Eight of the 12 cases were diagnosed as malignant before operation. Carcinoma associated with ulcerative colitis occurred from 10 to 15 years earlier than in the general population. The incidence of carcinoma in patients affected by ulcerative colitis for 10 years or more was much higher than in patients of the same age and sex who had not had it. The policy of earlier colectomy adopted in recent years has improved the prognosis of patients with ulcerative colitis who develop malignant growths in the colon or rectum. The presence of adenomatous polyps might well be added to the criteria to hasten the decision for radical surgery before the onset of malignant change. "Stricture" areas in chronic cases should be closely watched because strictures may prove to be the earliest evidence of malignant change. A carcinoma could easily be mistaken for an inflammatory stricture, and it is fre-

quently difficult to distinguish the two. Multiple carcinomas are frequently found in cases of malignant tumor associated with chronic ulcerative colitis. Contrary to reports that cancerous tumors associated with the disease are frequently atypical, the characteristics of carcinoma in this series tended to take on the general pattern of ordinary carcinoma of the rectum and colon. Malignant changes often appeared first in the quiescent stage of ulcerative colitis, when clinically the patient seemed to have improved.

Analysis of Five Year Survival in Carcinoma of the Rectum and Rectosigmoid. C. W. Mayo and O. A. Fly. Surg. Gynec. & Obst. 103:94-100 (July) 1956 [Chicago].

A comparison of the survival rates of 1,146 patients with carcinoma of the rectum and rectosigmoid is presented, with emphasis on the three operative procedures (anterior resection, one-stage combined abdominoperineal resection, and posterior resection) with which they were treated at the Mayo Clinic. The results of these survival studies in the controversial groups, that is, patients whose lesions are located between 6 and 15 cm. from the dentate margin, indicate that a sphincter-preserving procedure, such as anterior resection, is as curative as is one-stage combined abdominoperineal resection or two-stage posterior resection. No criticism can be made of the selection of a sphincter-sacrificing technique for lesions in the region of the anus and in the distal 5 cm. of the rectum. The grade of malignancy of the lesion was not a significant factor in this analysis, as the distribution was essentially the same in each group studied. There was no significant variation in the number of patients with or without nodal metastasis in the various segments of the rectum and sigmoid studied. The level of the lesion in relation to the peritoneal reflection has little influence on the survival rates.

Congenital Arteriovenous Fistulas in the Extremities: An Analysis of Sixty-Nine Cases. G. Coursley, J. C. Ivins and N. W. Barker. Angiology 7:201-217 (June) 1956 [Baltimore].

The authors define an arteriovenous fistula as "a vascular abnormality in which there are one or more direct or indirect communications between an artery and a vein without any intervening capillary bed." Such fistulas may be classified as either "acquired" (traumatic) or "congenital" in origin. Congenital arteriovenous fistulas may be located in almost any part of the body, but they are found most commonly in the extremities. The present paper is concerned only with congenital arteriovenous fistulas of the extremities, the treatment of which is known to be difficult and generally unsatisfactory. The clinical, laboratory, and therapeutic aspects of congenital arteriovenous fistulas seen at the Mayo Clinic in 69 patients during a 19-year period were evaluated. The arteriovenous shunts, invariably multiple, may be localized or, more commonly, diffuse. Excision of localized fistulas often produces good results, whereas it is very difficult or even impossible to eradicate diffuse fistulas and still preserve the limb. Associated involvement of bone results in recurrences of the fistulas after surgical treatment and frequently necessitates a major amputation of the affected limb. Partial surgical excision may alter the local hemodynamics so that actual or potential arteriovenous shunts open up at a more proximal level, giving rise to a recurrence, which necessitates further surgical treatment and very frequently leads to loss of the limb because of inability to preserve function in the limb.

Results of Surgical Treatment of Peptic Ulcer in Municipal Hospital of San Juan. R. Arredondo. Bol. Asoc. méd. Puerto Rico 48:162-168 (April) 1956 (In Spanish) [San Juan, P. R.].

Two hundred fifty-one patients with peptic ulcer were observed in the Municipal Hospital of San Juan from 1946 to 1955. In 63 patients an exploratory laparotomy was performed within the first five hours after the perforation of a gastric ulcer. The operation consisted of gastrorrhaphy or duodenorrhaphy in 55 patients and of subtotal gastrectomy in 5. Antibiotics and intravenous fluid were administered. A recurrence took place in four patients during the first six months. The patients had either a gastrectomy or a gastrorrhaphy. Fatal complications occurred in one. Follow-up observations were made on 43 patients, of whom 24 had no symptoms and 19 required a more definitive operation after failure of the treatment. Gastrectomy was performed on 188 patients of an average age of 48 years. Roentgen examination and an exploratory laparotomy revealed a duodenal ulcer in 146 patients, pyloric ulcer in 17, and gastric ulcer in 25. Subtotal gastrectomy was performed in 174 patients, total gastrectomy in 10, tubular gastrectomy in one, and gastroenterostomy with vagotomy in 3. Blood transfusion, intravenous fluid, and antibiotics were given these patients. Immediate complications were leakage from the duodenal stump in two patients, postoperative hemorrhage in seven, subphrenic abscess in one, phlebitis in four, hypostatic pneumonia in nine, and obstruction of anastomosis in three. There were no deaths. Late complications were marginal ulcer in three patients and late obstruction in nine. There were no late deaths. A follow-up study was made in 136 cases. The results of the operation were satisfactory. The following complications were observed: dizziness, perspiration, and general debility, which were transient; hypochromic anemia, which appeared in 9 patients and was controlled by drugs; and urgent defecation within 30 minutes after ingestion of food, which appeared in 17 patients and spontaneously disappeared within four or six months without any treatment. The patients gained weight (between 2 and 7 kg. [4.5 and 15.5 lb.]) after the operation.

Thromboangiitis Obliterans in Women: Gangrene; Blood Vessel Graft. T. Hiertonn, F. Lund and J. Philipson. Angiology 7:233-242 (June) 1956 [Baltimore].

Thromboangiitis obliterans is very rare in women. While the literature contains reports on thousands of men with this disease, only about 60 women with this disease have been reported. This paper presents observations on a 43-year-old woman with symptoms considered typical of thromboangiitis obliterans. She had severe peripheral arterial insufficiency and necrosis of the toes of the right foot. Amputation above or possibly below the knee joint was considered. Arteriography revealed a 10-cm. arterial obstruction in the femoral popliteal artery. Local resection and reconstruction of the arterial pathway with a venous graft led to rapid regression of the severe signs of ischemia and healing of the ulcers. The formerly incapacitated woman was in very good condition three and one-half years after the operation. In order not to overlook the possibility of this type of surgical therapy, it is important that a careful analysis of the arterial network be made in cases of peripheral arterial insufficiency. The result in this case demonstrates the importance of reconstruction of the main artery even in the presence of areas of occlusion in medium-sized and small distal arteries.

Treatment of Low-Back and Sciatic Pain by the Injection of Hydrocortisone into Degenerated Intervertebral Discs. H. L. Feffer. J. Bone & Joint Surg. 38A:585-592 (June) 1956 [Boston].

The local anti-inflammatory action of hydrocortisone and its value in reversing or blocking the inflammatory process in degenerative joint disease, tendinitis, tenosynovitis, and related conditions having been verified, it was deduced that hydrocortisone should have a like beneficial effect when injected into the acutely swollen intervertebral disk, if the process had not become irreversible; that is, if complete rupture had not occurred. Only one injection was made. The hydrocortisone solution and an iodopyracet solution were combined so that a nucleogram could be made at the same time the therapeutic solution was injected. The nucleogram served a dual purpose; the immediate condition of the disk was determined and the nature of the ensuing clinical response to the hydrocortisone could be evaluated and related to the state of degeneration of the disk. The patient lies in the flexed position on his side on the x-ray table, and the disk under investigation is centered for a lateral roentgenogram. The disk is punctured by inserting a 4-in., 22-gauge regional block needle through an anesthetized area 1.5 cm. lateral to the upper margin of the spinous process of the subjacent vertebra. Entrance into the annulus fibrosus is accompanied by a sensation of rubbery resistance; after piercing the annulus, the needle is inserted about one more centimeter. The two lower lumbar disks are punctured routinely unless there is a definite reason for not puncturing one in particular and unless there is a reason for

puncturing one at a higher level. With the needles in place, a lateral roentgenogram is made and the accuracy of the position of the needles for injection is verified. The material to be injected is made up in a syringe by mixing 3 cc. of a 35% solution of iodopyracet with 1 cc. of a solution containing 50 mg. of hydrocortisone. Each interspace is injected under moderate pressure, and the needles are withdrawn. Trunk movements are made to help diffusion of the solution.

The author presents the results obtained in the first 60 patients. The maximum follow-up period was eight months. Nucleograms of 55 patients demonstrated pathological lesions of the intervertebral disks. Thirty-seven patients experienced rapid remission of symptoms after injection of hydrocortisone; 18 failed to respond. Surgical exploration of the involved disks in 16 of the 18 failures demonstrated irreversible changes. These results suggest that the method not only permits rapid arrest of an acute intervertebral disk herniation but also demonstrates early which disks will require surgical intervention. This would prevent morbidity and economic loss.

The Osteogenetic Phases of Regeneration of Bone: A Historical and Experimental Study. W. Axhausen. J. Bone & Joint Surg. 38A:593-600 (June) 1956 [Boston].

During the early investigations of the regeneration of bone, there was a conflict between the osteoblastic theory and the induction theory. The work of Orell and Levander contributed evidence to both theories. In the experiments described in this paper, the osteogenetic significance of the soft-tissue components of bone—periosteum, marrow, and living cells of the bone canals—was established anew. Even in adults, the latent osteogenetic cells were brought to proliferation and function within several days by the activating influence of bone necrosis. In order to clarify the effect of the nonspecific connective tissue of bone substance, autogenous frozen-bone grafts covered with periosteum were transplanted into dogs. Up to the 14th day no evidence of bone formation could be found on histological examination. Histological evidence of necrosis of the periosteum is proof of the fact that the osteogenetic tissue was completely killed by freezing. Since new bone formation and delayed bone regeneration of the graft took place after some time (even up to 53 days), a transformation of the nonspecific connective tissue of the host into osteogenetic tissue must have taken place. Consequently, the osteoblastic and induction theories are combined into a unified concept. Bone regeneration occurs in two osteogenetic phases. The first and, physiologically, most important phase originates in the preexisting specific cells and begins after several days. The inception of the second phase, however, originating in the nonspecific connective tissue, requires several weeks. Both phases are stimulated by the activating influence of the bone necrosis.

Skeletal Cryptococcosis (Torulosis): Report of a Case and Review of the Literature. H. R. Gosling and W. S. Gilmer, Jr. J. Bone & Joint Surg. 38A:660-668 (June) 1956 [Boston].

The most common form of torulosis (cryptococcosis) in human beings is chronic meningoencephalitis with fatal termination. Infection of the skeletal system by this fungus is rare. The authors found records of 24 patients with the skeletal form of torulosis, but in 4 of these patients only the skull was infected and in 3 of these the involvement was secondary to the primary disease of the brain and meninges. Primary skeletal torulosis was confirmed in 18 patients. The authors report a new case of torulosis in a 10-year-old Negro boy who had injured his left knee in a fall from a bicycle two weeks before he was hospitalized. Greenish-yellow purulent material was repeatedly aspirated from the knee-joint. Penicillin, streptomycin, and hyaluronidase were injected locally. Several weeks later the patient began to complain of pain in the right elbow, and a swelling of the right sternoclavicular joint was noted. Roentgenographic examination revealed bone destruction in the medial end of the clavicle and an osteolytic lesion in the neck of the right radius. The diagnosis based on the pathological findings was chronic granulomatous osteomyelitis, probably torulosis (cryptococcosis). Cultures and animal inoculations corroborated this diagnosis. The boy recovered after surgical and antibiotic treatment of the bone lesions.

The authors gained the impression that the prognosis for patients in whom skeletal torulosis (cryptococcosis) is associated with "generalized" or meningeal involvement is poor. There have been no recorded survivals of such patients in spite of therapy. The prognosis for patients with localized bone lesions is good regardless of the therapy employed; however, surgical removal of the diseased bone will enhance healing and will lessen the possibility of dissemination of the disease.

Hypertension After Nephrectomy and After Intervention on the Extrarenal Urinary Region. G. Rallo. Clinica 16:165-175 (No. 3) 1956 (In Italian) [Bologna, Italy].

The author believes that surgical intervention is indicated in hypertensive patients with kidney affections. The operation should be performed as soon as possible in order to avoid irreversible kidney lesions. Nephrectomy was performed in 50 patients with hypertension and kidney lesions. Fifteen had tuberculosis, 12 hydronephrosis, 12 neoplasia, and 11 kidney calculosis. Results were good in 16 patients, or 32%; fair in 6, or 12%; and negative in 28, or 56%. The age and sex of the patient have no effect on the hypotensive results of nephrectomy. A drop in pressure, unless dependent on other causes, occurs only in those patients whose remaining kidney is free of lesions. Fifty hypertensive patients with extrarenal disease were also studied. Twenty had a prostatic tumor, 15 had calculosis of the urinary bladder, and 20 had pyeloureteral calculosis. Results were good in 63.6% of the patients, fair in 9.09%, and negative in 27%. Results were best when the damage to the kidney was in its acute stage. Obstruction that has existed for a long time creates an irreversible lesion in the adrenal parenchyma, and the arterial pressure does not drop even after the removal of the obstruction. In such cases and in cases of unilateral lesion, hypotension can be obtained by a nephrectomy.

Solitary Eosinophilic Granuloma of Bone. T. Hunter. J. Bone & Joint Surg. 38B:545-557 (May) 1956 [London, England].

Hunter reports on eight patients with solitary eosinophilic granuloma of bone. The fact that three were observed in one hospital during the past year indicates that the lesion is not extremely rare. Although the condition was established as a pathological and clinical entity in 1940, its etiology has not been clarified. It occurs chiefly in children and young adults, and, although the sex incidence in this small series of cases was equal, as a rule it occurs more often in males. The skull, ribs, femur, vertebrae, pelvis, mandible, humerus, and clavicle are most commonly involved. The main histological characteristics—sheet-like formation of histiocytes ("the basic component"); more or less conspicuous numbers of eosinophilic cells, especially of eosinophilic leukocytes; and actively phagocytic multinuclear giant cells—were observed in seven of the eight patients. In the remaining patient, eosinophilic cells were a less conspicuous feature, but their presence in focal collections against a background of fibroblasts and pale-staining cells with abundant vacuolated cytoplasm was sufficiently diagnostic of the eosinophilic granuloma group.

Clinically, eosinophilic granuloma may be a completely silent lesion. In three of the eight patients, symptoms were first noticed after an injury. None showed any significant systemic disturbance. Local pain is usually the presenting symptom, and swelling may occur if the lesion is in the long bones. Laboratory studies are of slight importance for the diagnosis, except that leukocytosis is occasionally detected; the erythrocyte-sedimentation rate may be raised, and eosinophilia has been recorded as an occasional finding but was not found in the present cases. Radiographically, the lesion presents as an area of endosteal destruction, irregular in outline, or with a smooth contour producing a "punched out" effect. As it enlarges, it eventually erodes the cortex, a section of which may disappear completely or partly. Subperiosteal new bone formation is regarded by most authors as unusual. When it occurs, it is said to be associated with perforation of the cortex. Four of the present patients showed subperiosteal new bone formation. The radiographs in one patient in particular showed well defined "onion-skin" layers resembling the classic description of

Ewing's tumor. Cortical perforation into the overlying soft tissues was observed at operation in only one of these patients, but all four showed radiographic evidence of complete destruction of parts of the original cortex.

As regards complications, the author says that the fracture occurring in one patient does not entirely merit such a description, since it occurred soon after a biopsy operation during which part of the femoral cortex had been removed. The radiographs of a second patient showed a crack fracture through the site of a clavicular lesion. The involvement of the nerve roots in a patient with profound motor weakness is of interest chiefly because of the rapidity of the disappearance of the paralysis. The prognosis of eosinophilic granuloma is favorable in that complete and spontaneous recovery of a lesion has been observed in patients with multiple foci. In view of the lack of specific diagnostic criteria short of biopsy, however, it follows that solitary eosinophilic granulomas of bone, once demonstrated radiographically, are likely to be explored. To curettage is then attributed the subsequent healing of the lesion. Diagnostic considerations and healing apart, curettage appears to fulfil an additional function in rapidly relieving the pain, probably by decompression of the lesion. Since resolution may occur either spontaneously or after curettage, the place of radiotherapy in the treatment of eosinophilic granuloma is difficult to assess. It was employed originally as an empirical measure, and, although most writers agree that it is successful in relieving pain, there is some doubt as to its actual effect on the pathological process.

NEUROLOGY & PSYCHIATRY

Cystic Astrocytoma of the Cerebellum, an Anatomoclinical Study of Forty-Four Cases with Operative Results. P. Wertheimer and M. Corradi. Semaine hôp. Paris 32:2179-2188 (June 22) 1956 (In French) [Paris, France].

The authors studied 44 cases of cystic astrocytoma of the cerebellum. The radiological, ventriculographic, and electroencephalographic characteristics of these tumors allow the diagnosis to be made before the occurrence of complications due to intracranial hypertension. Eighteen astrocytomas occupied the left lobe, 14 occupied the right lobe, 3 were in the vermis, 3 occupied both the vermis and a hemisphere, and 2 were limited to the fourth ventricle. The average duration of preoperative development was eight or nine months. Signs of intracranial hypertension are early symptoms. Signs of irritation of the centers of the floor of the fourth ventricle are less frequent. Headache, vomiting, vertigo, and disturbance of balance are frequently but not necessarily present. In 38% of these patients headache alone, almost always of an intermittent and paroxysmal nature, appeared in the beginning. Several of the patients were symtom-free for from three to four weeks up to several months.

At the height of the disease, headache, vomiting, and vertigo are paroxysmal but on a continuous basis. At this stage, when vomiting is present in 90% of the cases, signs of intracranial hypertension are confirmed by neurological examination and standard radiographs. Confusion is not an indispensable corollary of intracranial hypertension; only 3 of the 44 patients were confused. In 55% of the cases there were clinical signs of obstruction to the cerebrospinal fluid flow, notably collateral venous circulation in the forehead and upper eyelids. Hypotonia, a major sign (found in 18% of the patients), is almost always homolateral in relation to the lesion and is frequently localized in only one member. Signs of cerebral incoordination are always homolateral in relation to the lesion and occur most frequently in the lower members. Bilateral papillary edema was present in 27 patients. Stasis was almost always accompanied by a diminution of visual acuity, generally between ⅗ and ⅘. This examination is very important, but the absence of papillary edema does not eliminate possibility of a neoformation of the cerebellum. Labyrinthine symptomatology is especially evident in anterolateral cerebellar lesions compressing the nuclei or the vestibular roots. These signs, although disharmonious, must frequently be credited to a syndrome of intracranial hypertension. They rarely clarify the nature or extent of the causal lesion. The slow development of cystic astrocytomas and the frequency with which they appear in young subjects usually lead to changes in the cranium that make it possible to detect intracranial hypertension on radiological examination. The younger the patient and the slower the development, the clearer will be the signs of hypertension.

An electroencephalographic examination was made of 16 patients. Three kinds of signs were distinguished: false, suggestive in view of the clinical picture, and characteristic. The last-named type (25% of the cases) includes slow occipital unilateral waves not always on the side of the tumor and sometimes associated with slow bifrontal waves provoked by hyperpnea. Ventriculography permits confirmation of the clinical diagnosis of tumor of the posterior cerebral cavity. It frequently indicates exactly the hemispheric or vermian seat of the lesion and inproves diagnosis by giving information concerning the general state of the ventricular system. Clinical forms of astrocytoma may be subdivided into those of the child and the adolescent as opposed to those of the adult. The child or the adolescent is in good condition. If obnubilation exists, it is light. There are episodes of vomiting and headache. The cranium is slightly enlarged in volume, the posterior cavity may rise a little, the nape is stiff, and moving the head is painful and produces vertigo; pains, especially in the nape, radiate dorsally. Neurological examination shows a disharmonious cerebellar vestibular syndrome with cerebellar incoordination, often unilateral, accompanied by a paralysis of certain cranial nerves, especially of the sixth and seventh pair, and signs of moderate compression of the motor pathways with beginning papillary stasis.

Of the 44 patients operated upon at Lyon from 1932 to 1955, 7 died in the first days after the intervention. In two of these the tumor had invaded the cerebral trunk. In the following three months, nine died, five in a state of profound cachexia and four from respiratory disturbances. Fifty-six per cent of the patients operated on during the 12 years from 1932 to 1943 died, whereas, during the 12 years from 1944 to 1955, only 14% died. This illustrates the improvement of surgical technique and enrichment of experience. Neurological examination in 20 of the surviving patients is at present completely negative. Six recurrences at intervals of from 1 to 11 years after the first excision were reported.

Acute Hemorrhagic Encephalitis. K. Kristiansen, W. Harkmark and M. M. Cohen. Neurology 6:503-509 (July) 1956 [Minneapolis].

Kristiansen and associates discuss observations on five patients with acute hemorrhagic encephalitis who were observed in the seven-month period ending June, 1954, at a hospital in Oslo, Norway. The series included three men and two women ranging in age from 31 to 51 years. Headache or elevation of temperature preceded the neurological symptoms in most of these patients; in two a productive cough indicated a preceding upper respiratory infection. Symptoms of nervous system involvement then appeared and were often localizing. Hemiparesis and stupor were most common; hemihypesthesia, quadriplegia, central facial palsy, papilledema, nuchal rigidity, confusion, disorientation, hallucinations, diplopia, and dysphasia were less frequently observed. The results of laboratory tests were rather inconstant. The angiographic findings generally suggested a space-occupying lesion. The focal cerebral symptoms together with evidence of increased intracranial pressure and angiographic abnormalities led to surgical procedures in all five cases. Craniotomy and cerebral biopsy were performed in four patients in whom angiography exhibited displaced vessels. Three patients died during the acute disease and two survived. One surviving patient now presents only an incomplete left-sided hemianopsia despite his early hemiparesis, diplopia, disorientation, and stupor. The second survivor exhibited little improvement after the acute stage of illness. Progressive mental deterioration, disorientation, and confusion necessitate institutionalization.

The term acute hemorrhagic encephalitis was suggested by Strümpell in 1891 to describe a condition characterized pathologically by necrosis, hemorrhage, and demyelination in the cerebral white matter. In subsequent reports elaborating the pathological features of this disorder, the lesions were often noted to be asymmetric, with one hemisphere exhibiting more severe damage than the other. Although the pathological changes have been adequately described in fatal cases, the pathogenesis and the etiological agent remain unknown. This hemorrhagic

encephalitis has been known to occur in conjunction with viral infection, allergic reaction, and intoxication. The fact that the five cases presented in this paper occurred within a brief period of seven months suggests the possibility of toxic or infectious causation.

Current Status of Chlorpromazine and Reserpine in Psychiatric Practice. B. C. Schiele, R. W. Anderson and W. Simon. Journal-Lancet 76:179-185 (July) 1956 [Minneapolis].

Reserpine and chlorpromazine are the most widely used of the so-called "tranquilizers." These drugs induce a state of quietude with little or no clouding of consciousness, an effect that makes them the most useful preparations available for the management of acute states of excitement. Their use has resulted in a reduction of electroshock and insulin shock treatments and of lobotomy. These tranquilizers are less effective in the treatment of office than of hospitalized psychiatric patients. They facilitate psychotherapy, but they are not a substitute for it. Some patients do not obtain beneficial effects even when the drugs are given in large doses. While most patients tolerate either or both without difficulty, annoying side-reactions may occur, particularly with chlorpromazine. The action of reserpine appears to be slower, less potent, and less toxic. Chlorpromazine is preferred in the treatment of excited patients when rapid action is required. Neither drug seems to ameliorate states of depression. While many psychiatric patients have improved and some have been discharged, a large-scale emptying of state hospitals has not occurred. The drugs are more effective in acute than in chronic disorders. Although the fact that pharmacological agents are now available that relieve distressing symptoms for so many patients is very encouraging, the authors cannot conceive of any drug that will alter basic personality structure.

Diagnostic Suitability and Limits of Complement-Fixation Reaction in Patients with Poliomyelitis. E. Berger and M. Vest. Schweiz. med. Wchnschr. 86:776-778 (July 7) 1956 (In German) [Basel, Switzerland].

Complement-fixation tests according to Fulton and Dumbell's technique were performed on blood samples obtained from 98 patients with poliomyelitis associated with paresis, 103 patients with serous meningitis who were suspected of having poliomyelitis, 45 patients with various febrile infections not caused by the poliomyelitis virus, and 27 patients with afebrile diseases. A positive reaction of the blood to the test was obtained in 85 (86.7%) of the 98 patients with poliomyelitis associated with paresis. These results corresponded with those obtained by many other workers, although they may have used other techniques for the complement-fixation test. A positive reaction of the blood to the complement-fixation test was obtained in 47 (45.6%) of the 103 patients with serous meningitis of doubtful origin. The total number of positive reactions was obtained by testing a second blood sample with regard to the presence of complement-fixing antibodies from 7 to 12 days after a negative reaction of the first blood sample had been obtained at the end of the first week of the patient's disease. The number of positive results obtained under these conditions corresponded to those obtained by other workers who used the method of direct demonstration of virus by growth of the pathogenic agent in tissue culture.

The complement-fixation reaction is an aid in confirming the clinical diagnosis of poliomyelitis. The complement-fixation reaction is of particular value for the diagnosis of nonparalytic forms of poliomyelitis the cause of which is not clear. The diagnostic value of the complement-fixation reaction, however, has its limits, primarily because of the observation of negative reactions to the test in patients with a definite clinical aspect of poliomyelitis. A positive reaction to the complement-fixation test in the absence of clinical criteria for poliomyelitis was observed in 8 (11%) of the 72 patients with infections which were not caused by the poliomyelitis virus. Although inapparent infections with poliomyelitis virus may produce complement-fixing antibodies, it cannot be definitely stated that causative agents other than poliomyelitis viruses may not be responsible for a positive complement reaction. The complement-fixation reaction does not seem to be an appropriate means of establishing the type of the causative virus in patients with poliomyelitis.

GYNECOLOGY & OBSTETRICS

Non-Suppurative Osteitis Pubis in the Female. L. L. Wiltse and C. H. Frantz. J. Bone & Joint Surg. 38A:500-516 (June) 1956 [Boston].

The authors report the occurrence in 13 women of a disease that they believe is a definite clinical entity related to, but not identical with, osteitis pubis in men. The disease was nonsuppurative and noninflammatory and developed in the anterior portion of the pelvic girdle. In five of the women, the symptoms were first noted during pregnancy; in five others, the symptoms appeared within two months after delivery; in one, they appeared after extensive pelvic surgery; and in two they developed after an injury. Four illustrative case histories are presented, one from each of these four groups.

The typical patient with this disease (usually a young woman) begins to experience pain about the symphysis within a few months after the occurrence of some event capable of producing trauma in the adjacent structures. A physical examination reveals tenderness directly over the symphysis, although no swelling or fluctuation is seen. Blood, urine, and temperature are generally normal, but the symphysis frequently shows instability. The pain often becomes so severe that the woman is completely bedridden and can neither sit nor stand. As the disease progresses, the roentgenograms may show spotty demineralization of the bone adjacent to the symphysis, widening of the symphysial gap, and gradual development of sclerosis and narrowing. The disease is self-limited, but it may persist for weeks or years. Treatment was symptomatic in all of the 13 patients presented. It consisted of bed rest, warm packs, and analgesics. One of the patients who had been attended by a number of doctors received a variety of treatments, including x-ray therapy, corticotropin, cortisone, and phenylbutazone. The authors comment on osteitis pubis in male patients and present their own concept of the etiology, which admittedly leaves some factors unexplained. They believe that the condition referred to as osteitis pubis is a localized reflex neurovascular dystrophy brought about by a combination of trauma and predisposing changes at the symphysis. The changes at the symphysis are due to the influence of certain hormones and are of the nature of, but more pronounced than, those that normally occur during pregnancy.

Recent Research in Physiology of Breast Applied to Mammary Cancer. G. Hadfield. Brit. M. J. 1:1507-1511 (June 30) 1956 [London, England].

According to Hadfield, about 50% of human breast cancers are hormone-dependent and do not have the gloomy and mysterious attribute of "autonomy" so often regarded as the essential biological characteristic of all malignant tumors. A breast cancer is said to be hormone-dependent if progressive proliferation of its infiltrating and metastasizing cells is conditioned by an adequate supply of the specific mammotropic hormones responsible for physiological mammogenesis. The author reviews experimental studies on the hormonal control of the breast and discusses the presence of mammotropic hormones in the urine. Normal breast growth is controlled by the synergistic action of the pituitary hormone prolactin acting at a relatively high concentration, with ovarian estrogen acting at a relatively low one. Combined oophorectomy and adrenalectomy deprive the breast cancer of estrogenic steroids, and growth regression follows if the tumor is hormone-dependent. This effect seems to be almost always temporary; estrogen production is slowly reestablished, and progressive growth of the tumor recurs, probably when estrogen production from an unknown site reaches the low level required for normal mammogenesis. Total hypophysectomy in all probability completely deprives the tumor of estrogen and prolactin. This operation can have no effect on the growth of a hormone-independent tumor. The urine of all premenopausal women and of approximately 50% of postmenopausal women contains one or more mammotropic hormones. It seems probable that it contains prolactin. If the urine of a breast-cancer patient has no mammotropic activity, it seems very probable that her cancer would not be hormone-dependent and that hypophysectomy would have no effect on its progressive growth.

Further Experience with Apresoline in Toxemia and Hypertension of Pregnancy. H. L. Riva, W. L. Pickhardt, R. H. Holzworth and R. L. Sherman. Am. J. Obst. & Gynec. 72:48-55 (July) 1956 [St. Louis].

Results of 1-hydrazinophthalazine (Apresoline) therapy in 67 pregnant toxemic and hypertensive patients are presented. The patients were divided into the following groups: preeclampsia, hypertension of labor, hypertensive vascular disease, hypertension with superimposed toxemia, eclampsia, and preeclampsia with chronic glomerulonephritis. The mean vasodepressor response was significant in all six groups; it was less marked in the patients with a previous history of hypertension. The average tachycardia after administration of Apresoline was noted within 30 minutes and amounted to an increase of about 20 to 30 mm. Hg. The infant mortality, amounting to about 7%, was not attributed to the use of Apresoline. Oral or subcutaneous administration may have a place in a few selected nonacute cases. The intravenous drip method of administering Apresoline was found to be the most efficacious in maintaining a desired lowering of blood pressure and so avoiding a precipitous drop in blood pressure. Apresoline is highly recommended for the control of the hypertensive aspects of preeclampsia and hypertension in pregnancy.

Comments on the Richardson Pregnancy Test and the Rapp-Richardson Saliva Prenatal Sex Determination Test. W. G. Dobson and A. G. Gornal. Am. J. Obst. & Gynec. 72:70-74 (July) 1956 [St. Louis].

The Richardson pregnancy test is questioned both as to its reliability and the theoretical basis on which it was proposed. The authors obtained an accuracy of about 75% in pregnant patients and 47% in nonpregnant women. Evidence is presented that the method of extraction does not effect any separation or purification of an estrone fraction and that, even if it did, the amount of free estrone in the urine of pregnant women is much too small to be detected with 2, 4-dinitrophenylhydrazine. The Rapp-Richardson saliva prenatal sex-determination test is subject to similar criticism and had an accuracy that indicated that the result was in no way determined by the sex of the fetus.

Fertility After Tubal Pregnancy. S. Bender. J. Obst. & Gynaec. Brit. Emp. 63:400-403 (June) 1956 [London, England].

Two hundred sixty-four of 305 women who had been operated on for tubal pregnancy between 1946 and 1952 were followed up. One or more pregnancies occurred after this operation in 116, or 44%, of these 264 women. On the basis of this follow-up, it appears that, of each 100 women who have had tubal gestations, 56 do not conceive again and 44 do. Of the 56 who remain sterile, 7 have had a sterilizing operation. In another six, the remaining tube has been shown by salpingography to be blocked. There must be others in whom the remaining tube is blocked, but the fact has not been proved. In addition, at least 3 of the 56 do not become pregnant because they consistently practise contraception purely for fear of another ectopic pregnancy. Doubtless there are others who practise contraception for other reasons. In 44 of 100 conception does occur again; but this is a minimum figure because of the limited time of follow-up, at the most seven years. If all of these women were followed to the menopause, the conception rate would probably approach 50%. Of the 44 who do conceive, 32 produce live babies. This means that only one in three women who have had a tubal pregnancy will thereafter have a live child.

The conception rate was notably higher in the 130 women under the age of 30 at the time of operation (54%) than in the 134 older patients (34%). The conception rate was the same in the previously parous and the previously nulliparous. Of particular interest is the relationship between the type of operation performed and the subsequent conception rate. Nothing was done at laparotomy in four women, because tubal abortion was seen to be complete; all four became pregnant again. This is a reminder that probably most cases of tubal pregnancy are never diagnosed. Probably the commonest fate of the fertilized egg that implants in the tube is that it dies and is absorbed. Of four women on whom salpingotomy was performed, three became pregnant again. In the majority of cases (187) salpingectomy was carried out, and 80 of these women became pregnant again, a conception rate of 42.7%. In 51 women, salpingo-oophorectomy was performed, and 29 of these became pregnant again, a conception rate of 56.8%. Statistically, the difference between these rates is barely significant, but the author cites evidence indicating that pregnancy is more likely to occur again when tubal pregnancy is treated by the removal of both tube and ovary rather than the tube alone. Inspection of the nonpregnant tube for patency, salpingotomy instead of salpingectomy when feasible, but salpingo-oophorectomy when salpingotomy is not possible, are cited as the chief measures to be taken in women who wish to become pregnant again after a tubal pregnancy.

Tuberculosis and Pregnancy. S. Jacobs. Dis. Chest 30:43-49 (July) 1956 [Chicago].

The author studied a series of 64 tuberculous women who received obstetric care at the Charity Hospital of Louisiana. Most of them were young Negro women receiving antibiotic therapy. It was found that pregnancy does impose an additional stress on tuberculous women, but quantitative evaluation of this stress is almost impossible. Most women, particularly those who are anxious to have children, can tolerate this stress when treated with the antibiotics currently available. To reduce this stress to the minimum, tuberculous women should be advised to defer pregnancy until the disease has been inactive at least two years if minimal, three years if moderately advanced, and five years if far advanced. Experience with a relatively small group suggests that, if this precaution is observed, even multiple pregnancies are tolerated without reactivation of the tuberculosis. To detect tuberculosis, each obstetric patient should have a chest x-ray film examination as soon as pregnancy has been discovered. When tuberculosis is found in a pregnant woman, treatment with antibiotics and rest should be started at once precisely as during the nongravid state. Other methods of therapy should be added as needed. The patient may be assured that, with adequate therapy, she will continue to improve despite the pregnancy, may be delivered of a normal child, and will be noninfectious by the time of confinement.

PEDIATRICS

Prevention of Extension of Tuberculosis in Early Childhood. P. Zoelch. Deutsche med. Wchnschr. 81:1082-1084 (July 6) 1956 (In German) [Stuttgart, Germany].

To ascertain the value of isoniazid in preventing the dissemination or generalization of tuberculosis, the author sent questionnaires to 15 children's clinics and to 5 sanatoriums for tuberculous children. The question whether isoniazid prevents generalization of tuberculosis was generally answered in the affirmative. Particularly impressive was the fact that isoniazid given by mouth prevented threatening meningitis in young children with miliary tuberculosis. Only two children were mentioned in whom meningitis resulted from miliary tuberculosis, whereas before the introduction of isoniazid tuberculous meningitis developed in about 50% of the children with miliary tuberculosis of the lungs. The author also learned of five children in whom tuberculous meningitis developed after other forms of tuberculosis, while they were being treated with isoniazid. In his own sanitarium the author observed a young child with tuberculous pneumonitis and caseous degeneration in whom fatal tuberculous meningitis developed after three months of combined administration of isoniazid and streptomycin. In two other patients with tuberculous lung infiltrations, meningeal symptoms developed temporarily during isoniazid therapy. The author believes that in these two patients tuberculous meningitis would doubtless have developed in the absence of the administration of isoniazid. Miliary tuberculosis rarely developed during isoniazid therapy.

The question of the occurrence of hematogenous dissemination of other forms during isoniazid therapy was answered variously. Skeletal, pleural, renal, and lymph-node involvements were occasionally observed, but there was always the possibility that these disseminations existed before the isoniazid therapy was begun. The toxic effects of isoniazid were mostly minor and

easily reversible. To determine whether invasion and breakdown of the bronchial lymph nodes occurs more frequently with than without isoniazid therapy, the incidence of recurrent pulmonary exacerbations, which, like aspiration infiltration, atelectasis, and mixed forms, are often caused by perforation of lymph nodes, was investigated. The incidence of these complications with and without isoniazid therapy differed in various institutions, but the author believes that differences in case material existed and that pulmonary recurrences were not essentially greater with than without tuberculostatic therapy. As regards the age of the patients who should receive isoniazid therapy to prevent dissemination of tuberculosis, it is advisable in children under 2 years of age but not in those over this age. The beginning dose is 5 mg. per kilogram of body weight, and this is later increased to 10 mg. per kilogram. Periods of treatment lasting one month are followed by a treatment-free interval of equal length, and in this way isoniazid therapy may be continued for one year.

Myeloid Leukemia in Children. P. Giraud, R. Bernard, T. Mangipan and F. Challiol. Semaine hôp. Paris 32:2444-2451 (July 10-14) 1956 (In French) [Paris, France].

The authors observed myeloid leukemia in three boys aged 11, 5, and 13. They cite some manifestations of the disease, rare in children, that are more frequent in the child than in the adult: (1) ocular involvement, found in two of the cases, in the form of classic retinitis with papillary edema, small punctate and juxtapapillary hemorrhages, large venous bilateral congestion, and white perivascular infiltrates; (2) moderate renal attack manifesting itself by a simple and relatively frequent albuminuria; (3) cutaneous lesions the size of a pea to that of a nut, violet-colored and histologically characteristic; and (4) generalized or localized adenopathy, sometimes microulcerated. Apart from these relatively rare manifestations, the clinical aspect of myeloid leukemia in children does not differ notably from that found in adults with this disease. In infants the disease may be mistaken for the Von Jacksch-Suzet syndrome. The basic clinical feature is splenomegaly, and the blood picture commonly shows the presence of anemia and platelet deficiency. The total course of the disease toward a fatal end rarely seems to exceed three years. The terminal complication usually consists of hemorrhages with leukoblastic transformation. Death was due to cerebral thrombosis in one of the three reported cases. Although no newer form of chemical therapy has as yet been tested in the child, such therapy might possibly afford a longer survival time in this fatal affection.

The Immunization of Allergic Children: Part I. Special Reference to Eczema Vaccinatum. B. A. Johnson and S. C. Dees. North Carolina M. J. 17:304-309 (July) 1956 [Winston-Salem, N. C.].

Eczema vaccinatum is a preventable disease. Eight cases occurred in 415 cases of atopic eczema, representing about 2 cases of eczema vaccinatum among each 100 cases of eczema. All the patients were 5½ years of age or younger, and death occurred in the case of a 6-month-old infant. The vaccinated 5-year-old and 6-year-old preschool and school-aged sibling constitutes the greatest single menace as a contact with the eczematous child. A vaccinated person should be considered a danger to the eczematous child until the scab from the vaccination site has fallen. The history of contact with a vaccinated person is the most valuable aid to the physician in the diagnosis of eczema vaccinatum. The authors urge adherence to the contraindications of smallpox vaccination. Persons who have a skin disease or who are intimate contacts of a person with a skin disease should never be vaccinated.

Pheochromocytoma in a Thirteen-Year-Old Child. P. Giraud, M. Salmon, R. Bernard and others. Semaine hôp. Paris 32:2435-2440 (July 10-14) 1956 (In French) [Paris, France].

The authors report the case of a 13-year-old child who showed permanent arterial hypertension. Diagnosis of the presence of a pheochromocytoma was confirmed by the Regitine test. The tumor was removed and the child recovered. The authors analyze a number of reports in the literature of pheochromocytoma in children. Hypertensive paroxysmal crises are rare because this tumor usually produces permanent hypertension in children. Retropneumoperitoneum is very helpful in the diagnosis of pheochromocytoma, but its interpretation may be difficult. Pharmacodynamic tests are simple and more reliable. When they are positive the presence of an adrenalin-secreting tumor is confirmed. Of these tests, the one with Regitine is particularly recommendable, as it is reliable and innocuous. The only treatment for such tumors is surgical removal, which carries a high death rate as a result of operative accidents, paroxysmal hypertension, or postoperative collapse. Complete and definitive recovery may be expected after the surgical operation if such accidents are avoided.

UROLOGY

Simple Renal Cysts in Children: Review of the Literature and Report of Five Cases. J. H. DeWeerd and H. B. Simon. J. Urol. 75:912-921 (June) 1956 [Baltimore].

The present report is concerned with congenital simple (serous) cysts of the kidney occurring in childhood. Although these cysts are found fairly frequently at postmortem examination (2 to 4%), they rarely attain sufficient size to become clinically evident during childhood. Congenital simple renal cyst in children has been diagnosed clinically and treated in five patients at the Mayo Clinic since 1915. A table lists the important data on these five children and on 16 others described in the literature. All 21 patients met the following criteria: (1) the cyst was unilocular; (2) there was no communication between the cavity of the cyst and the renal pelvis; (3) the cavity of the cyst was lined with epithelium; (4) no renal elements were contained within the cyst; (5) a localized region of the kidney was involved; (6) the uninvolved renal tissue was relatively normal grossly or microscopically, or both, and (7) the renal pelvis and ureter were patent. Some cases included in previous studies were excluded from this study on the basis of these criteria.

Simple renal cyst is found somewhat more frequently in males and in the left kidney. It may be encountered at any age from the newborn period through adulthood, and it involves the poles of the kidney with approximately equal frequency. The presenting complaint in almost all cases is that of abdominal mass, occasionally accompanied by pain. The lesion is demonstrable by urography, either excretory or retrograde, but roentgenographic or clinical differentiation from embryonal carcinosarcoma (Wilms' tumor) is practically impossible. For this reason, and because simple renal cyst in children is rare as compared with renal embryoma (Wilms' tumor), the usual preoperative clinical impression is that of malignant disease. Excision of the presenting cyst wall is the treatment of choice unless severe destruction of renal parenchyma necessitates nephrectomy. Unfortunately, such destruction frequently prevails.

Urinary Tract Calculi in Poliomyelitis. J. R. Taylor, A. J. W. Alcock and J. A. Hildes. Canad. M. A. J. 75:29-34 (July 1) 1956 [Toronto, Canada].

A total of 1,390 patients with acute poliomyelitis were admitted to the Winnipeg Municipal Hospital during the three years from 1952 to 1954. Motor paralysis of the bladder, resulting in acute urinary retention, was a common accompaniment of low spinal paralysis. Approximately 300 patients required catheter drainage for varying periods of time for this reason. Although complete detrusor paralysis was transient, return of bladder function often took several weeks and was sometimes incomplete, as shown by cystometrography carried out on a few of the patients. Initially, Zephiran (benzalkonium chloride) in a 1:20,000 solution was used as a bactericidal irrigant in patients with indwelling catheters, but on this regimen incrustations frequently formed on the catheter and sometimes became the nidus for bladder calculi. In nine patients, bladder calculi were crushed and removed transurethrally and in three patients suprapubic lithotomy was carried out. When "G" solution was adopted as a routine bladder irrigant, bladder calculi were effectively prevented from forming and a few already

present were dissolved. A low-grade cystitis was common in patients with indwelling catheters, but this subsided once the catheter was removed.

Renal calculi proved to be the most important and the most troublesome of the urinary tract complications in patients with poliomyelitis. Artificial respiration was necessary in 237 patients. Respirator treatment for less than 40 days was necessary in 74 patients and for long periods in 98. Renal stones developed in 33 (about a third) of those requiring long-term respirator treatment and in one of those receiving short-term respirator treatment. No renal stones were found in the group not treated in a respirator. As in patients with prolonged recumbency for any reason, the authors consider immobility, with resulting demineralization of bone, and hypercalciuria the major factors in the development of renal stones. The calculi were typical radiopaque recumbency calculi of the soft triple-phosphate type. They were usually multiple and often bilateral, but there were several instances of solitary calculi or of involvement of only one kidney with multiple calculi. The stones varied greatly in size, from minute particles to stones of up to 2 or 3 cm. in diameter.

Repeated x-ray examinations are necessary throughout the whole period of recumbency. Although the usual prophylactic measures must be modified on account of the dependence on artificial respiration and severe extensive lower motor neurone paralysis, increased activity, weight-bearing, high urinary output, restricted calcium intake, and control of gross infection are important prophylactic measures. Multiple small and moderately large stones will often pass spontaneously. Stones in the lower ureter can be removed by transurethral manipulation in spite of some difficulties in cystoscopy caused by contractures and stiffness of hips and knees. When surgery on the kidney or ureter is necessary, it can be carried out with relative safety and with good results. Seventeen operations for renal calculi were carried out in 16 patients.

The Surgical Spread of Cancer in Urology. P. Boreham. Brit. J. Urol. 28:163-175 (June) 1956 [Edinburgh, Scotland].

Boreham believes that three of the following four criteria should be satisfied if a metastasis is to be considered an implant: 1. It must be discontinuous with the primary tumor, and therefore cannot have arisen by direct extension. 2. The growth must arise in another direction than that of the lymph drainage of the primary tumor. 3. It must arise in a tissue not normally the seat of blood-borne metastases. 4. The metastasis should preferably be growing in a tissue foreign to the type cell of the tumor.

Six cases of recurrence of carcinoma of the bladder occurring in the urethra are presented. Three of these were in the posterior and three in the anterior urethra. Another five patients are presented in whom metastases developed in the prostatic cavity after a prostatectomy had been performed in the presence of a carcinoma of the bladder. Fifteen patients with recurrence of carcinoma of the bladder in the scar of an open operation are discussed. It was found also that after approximately 3% of open operations on the bladder the first recurrence was in the scar. Although the evidence that these metastases arose by implantation is not conclusive in all of the cases, it is quite clear that surgical implantation does occur and that in some cases a surgical implant is the only metastasis that spoils an otherwise curative operation.

Bladder Involvement in a Case of Herpes Zoster. M. Dales and G. Wilson. Brit. J. Urol. 28:198-200 (June) 1956 [Edinburgh, Scotland].

A 42-year-old man was admitted to hospital with retention of urine of 12 hours' duration. During the preceding week he had been confined to bed with an upper respiratory infection. Four days prior to admission a painful rash had developed over his right buttock and thigh, and for 24 hours he had complained of intermittent suprapubic pain and increasing difficulty in micturition. Pressure in the suprapubic region produced intense pain and increased his desire to micturate. The prostate and urethra were normal. A typical zosterian eruption was present over the right buttock and thigh in the areas of the first and second lumbar dermatomes. Catheterization was performed and produced 300 ml. of clear urine. A course of aureomycin was given for the herpes zoster. Retention of urine recurred after the initial catheterization. Closed, continuous catheter drainage was used for 48 hours, after which the patient voided urine normally. Six weeks after discharge the patient remained well and had had no further urinary symptoms. There was a slight brownish pigmentation over the area of distribution of the rash, but there was no sensory loss, no muscle wasting, and the reflexes were normal. This case differs from those described elsewhere in that the lumbar segments of the cord were involved and no vesicles were found in the bladder or urethra. The disturbance appears to have been primarily a motor dysfunction. Recorded cases of bladder involvement in herpes zoster are remarkably few, a finding which is surprising in view of the relative frequency of bladder dysfunction in similar virus diseases of the nervous system, such as poliomyelitis.

OPHTHALMOLOGY

Retinal Lesions in Hodgkin's Disease. M. Brihaye-van Geertruyden A.M.A. Arch. Ophth. 56: 94-99 (July) 1956 [Chicago].

The author was able to follow for three months the evolution of cotton-wool opacities in the retina of a 31-year-old woman with Hodgkin's disease. The lesions were first noticed when the patient entered the hospital during a febrile episode. During the following days, new spots developed. As soon as cervical and splenic x-ray therapy was begun the retinal lesions progressively faded and no new lesion appeared, but 18 days after the end of the treatment new white spots appeared with hemorrhages. The number increased until death. The histological examination at autopsy proved that the cotton-wool opacities were conglomerates of cytoid bodies in the nerve-fiber layer of the retina. Although cotton-wool opacities have been observed in many diseases, the author was unable to find any other report on their occurrence in Hodgkin's disease. In conclusion she stresses the following points: 1. Cotton-wool opacities do not necessarily represent an infiltration by the specific tissue of Hodgkin's disease. 2. No parallelism existed between the appearance of cotton-wool opacities and the degree of anemia, hepatic damage, or biliary-tract disease. The evolution of cotton-wool opacities closely followed the general condition of the patient. Ocular examinations of other patients with Hodgkin's disease might throw additional light on the pathogenesis of this curious lesion.

Some Ocular Sequelae of Tuberculous Meningitis: A Preliminary Survey, 1953-54. A. J. Mooney. Am. J. Ophth. 41: 753-768 (May) 1956 [Chicago].

With modern therapy (streptomycin, aminosalicylic acid, and isoniazid) the survival rate in tuberculous meningitis is now about 80% and, as a result of this, eye complications that were practically unknown seven years ago are now a frequent occurrence. Within the past 15 months the author has examined 65 patients with tuberculous meningitis, of whom 47, or 72%, had ocular lesions. The pathological process appears to be tuberculous arachnoiditis that causes either papilledema by interfering with the circulation of the cerebrospinal fluid or pale disks by strangulating the pial vessels going to the optic nerves and chiasma. There was no connection between the amount of intrathecally administered streptomycin and the eye manifestations. No relationship could be established between deafness and eye complications.

The author believes that choroidal tubercles can be regarded as evidence of miliary tuberculosis. As a result of studying 16 patients with choroidal tubercles, he formed the opinion that the tubercles are a valuable prognostic guide; new tubercles appear when the disease is active, but when pyrexia subsides no fresh tubercles appear. Many smaller tubercles disappear without leaving any ophthalmoscopic evidence.

Papilledema was present in 17 patients, in some of whom the edema was confined to the upper and lower disk margins and subsequently disappeared as the disease regressed. In other patients the swelling amounted to two or even three diopters and the papilledema in these seemed to be of two varieties. In the first variety the disk showed a pale serous-looking swelling not necessarily associated with a high cerebrospinal fluid

pressure. This type of edema subsides as the disease is controlled, and improvement seems to be accelerated by repeated spinal punctures. The edema seems to be caused by external hydrocephalus, and the process is reversed as the meningitis subsides. In the second type of papilledema the disk presents the florid appearance typical of increased intracranial pressure from brain tumor or internal hydrocephalus. Antibiotics and repeated spinal punctures fail to control the swelling, and the author believes that papilledema of this type may go on to secondary atrophy if steps are not taken in time to relieve the increased intracranial pressure. Apparently the tuberculous basal meningitis causes adhesions in the posterior fossa that obstruct the flow of the cerebrospinal fluid from the fourth ventricle into the cisterna magna with resulting internal hydrocephalus. Neurosurgery was carried out in four of these patients.

Pallor of the disks with clear margins was present in 13 of the patients. Eight of these 13 patients were transferred to the neurosurgical unit for exploration of the optic nerves and chiasm in the hope of finding adhesions interfering with the blood supply of this part of the visual pathway, the removal of which would either improve the vision or prevent it from getting worse. The need for neurosurgery seems to be influenced to some extent by the time that has elapsed before treatment is instituted. When a practitioner is in doubt about diagnosis in a case of this nature, the patient should be sent immediately to a suitable hospital for treatment. A short course of cortisone therapy (in the absence of serious pulmonary complications) should be started and continued for about three weeks, with a view to preventing the formation of adhesions. A long course is not justified. If this treatment fails to prevent papilledema or pale disks, a careful watch should be kept on the disks, and, if they deteriorate in spite of treatment, neurosurgery seems justified.

Pigmentary Retinal Lipoid Neuronal Heredodegeneration (Spielmeyer-Vogt Disease): The Neuro-Ophthalmologic Considerations. J. Hoffman, Am. J. Ophth. 42: 15–21 (July) 1956 [Chicago]

The identification of many neurological disorders is facilitated by ophthalmoscopic examination. One entity that exemplifies this fact is Spielmeyer-Vogt disease, which is also known as Batten-Mayou disease, juvenile Tay-Sachs disease, juvenile amaurotic family idiocy, and cerebromacular dystrophy. On the basis of intensive research and critical analysis of the numerous papers on the subject as well as of independent clinical and laboratory studies, Hoffman and his co-workers believe that Spielmeyer-Vogt disease is a separate entity, distinct from not only the systemic lipoidoses but also the infantile type of Tay-Sachs disease. The differences far exceed the resemblances, which are superficial at best. Clinically, Spielmeyer-Vogt disease is manifested by an heredofamilial predisposition as a Mendelian recessive. About the fifth to eighth year of life there are suggestive symptoms indicating visual impairment. After an intellectual arrest, there is an almost precipitous drop. Organic psychological changes, such as irritability, apathy, and speech abnormalities, accompany this decline and are associated with numerous indications of a deteriorating central nervous system. Upper and lower motor neurone palsies, with or without grand mal and/or Jacksonian convulsions, are observed in varying combinations. One of the earliest changes observable on ophthalmoscopy is a yellowish-gray appearance of the retina, with slightly narrowed blood vessels. Gradually, small pigmented granules make their appearance at the periphery and in the course of time proceed centrally, eventually giving the entire retina an appearance resembling that in retinitis pigmentosa. Shortly after these changes have begun to show up, a macular alteration is noted and with it an expanding central scotoma. In sharp contrast to the "cherry-red spot" macula of Tay-Sachs disease, in Spielmeyer-Vogt disease there is a central brownish, brick-red core at the macula region. This is surrounded by a pale ring and then a halo of peppery pigmentation. The disk itself becomes extremely pale and presents a primary atrophic picture only late in the progress of retinal alterations.

The histories of two sisters with so-called Spielmeyer-Vogt disease are presented. The author suggests that a more appropriate, accurate, understandable, and meaningful name for this entity would be "lipoid neuronal pigmentary retinal heredodegeneration." It would eliminate the proper name confusion (Spielmeyer-Vogt, Batten-Mayou, Stengel, and so forth). It would separate this disease entity from the group of amaurotic family idiocies, since, technically speaking, it is a dementia rather than an amentia, as implied by the term idiocy. This new name would also do away with the limitation of the incomplete term "cerebromacular dystrophy." The name suggested indicates that the disease is a degenerative process of a hereditary nature and involves the neuronal elements and is associated with an inclusion lipoidal deposit. It presents another distinguishing feature, namely, the involvement of the pigmentary as well as the neuronal elements of the retina.

THERAPEUTICS

The Chemotherapy of Hypertension. R. Birchall, G. F. Weber and H. M. Batson. Am. Pract. & Digest Treat. 7:1104-1110 (July) 1956 [Philadelphia].

The results of the use of the newer chemotherapeutic agents in the treatment of 81 closely followed patients with various types of hypertension were evaluated in an effort to form definite impressions as to the usefulness of these preparations. The drugs employed included hexamethonium, hydralazine, veratrum, the derivatives of rauwolfia serpentina, and the newer ganglionic blocking agents, ansolysen and ecolid. Results were intentionally not evaluated on the basis of statistical analysis. Subjective as well as objective improvement and consideration of the emotional response of the patient to each regimen were the bases of evaluation. All patients with malignant hypertension or severe essential hypertension should be hospitalized for careful regulation of the blood pressure by the administration of a combination of a ganglionic blocking agent and reserpine. They should be taught to take their own blood pressures at home and to regulate the dosage of the ganglionic blocking agent by means of a sliding scale, depending on the blood-pressure reading taken at intervals that vary with the particular ganglionic blocking agent used. In patients with malignant hypertension, the blood pressure can almost always be controlled and the course of the disease "reversed" if renal function is good and the blood urea nitrogen level is below 40 mg. per 100 cc.

The authors have all but abandoned use of hydralazine, since it seems to have little advantage over reserpine and is more toxic. The toxic level of veratrum is so close to the therapeutic level that it is rarely considered useful. The effect of the rauwolfia derivatives is unpredictable. In patients who have previously had bilateral sympathectomy, they are potent antihypertensive agents and must be given cautiously and in small dosage initially. Of the ganglionic blocking agents, ansolysen is no more effective than hexamethonium, but the side-reactions are fewer and the regimen considerably easier. Ecolid has recently proved to be just as effective as ansolysen and will replace it as the agent of choice because of its smoothness of action and the convenience of administration at roughly 12-hour intervals as opposed to the ansolysen schedule, i. e., before meals and at bedtime. Experience with inversine is still too limited to permit any decision as to whether or not it will prove superior to ecolid.

Pharmacological and Clinical Research on O-Acetylsalicylamide. O. Piccinelli and A. Fiocchi. Gaz. med. ital. 115:139-146 (May) 1956 (In Italian) [Turin, Italy].

The authors carried out pharmacological and clinical research on O-acetylsalicylamide. The drug has no toxic effects; it is easily tolerated, and it has a marked corticotropic effect. One hundred forty-eight patients with rheumatism, fever, and various pains were treated with the drug. Dosage varied from 1 to 2 gm. per day given orally in divided doses of from 0.1 to 1.5 gm. at a time. Tolerance was perfect. Large doses caused some drowsiness. Gastric tolerance was very good, even in patients with gastrointestinal affections. Blood pressure remained within normal values. There were no kidney complications. Results were good in five patients with rheumatism. With daily doses of from 10 to 12 gm. fever disappeared within four to seven days. Results were not so good in 8 patients with rheumatic arthritis. In some patients symptoms were attenuated, but radiological observation did not show any improvement. Ten patients with

muscular rheumatism recovered completely. The drug has a marked analgesic effect. Neurological affections were checked in one or two days. The antipyretic effect was poor in six cases of typhus and two cases of brucellosis. The effects were good in 11 cases of pleuropulmonary affections: both symptoms and fever were checked.

Clinical and Laboratory Studies of Novobiocin, a New Antibiotic. W. M. M. Kirby, D. G. Hudson and W. D. Noyes. A. M. A. Arch. Int. Med. **98**:1-7 (July) 1956 [Chicago].

Laboratory studies of novobiocin, a new antibiotic, showed that micrococci (staphylococci) were remarkably sensitive to the drug in vitro and there was no cross resistance with other antibiotics. Pneumococci and group A streptococci were also inhibited by low concentrations of novobiocin, but they were less sensitive than micrococci. Among the gram-negative bacilli, members of the Proteus group were moderately sensitive. Novobiocin was less effective in the presence of a larger inoculum of bacteria, and serum exerted a pronounced inhibitory effect. Concentrations of novobiocin in the serum of patients receiving 2 gm. of the drug daily were considerably higher than those obtained with other antibiotics, but these levels were determined by a serial dilution method in broth and did not reflect the factor of serum inhibition.

Thirty-five patients with bacterial pneumonia, 26 with micrococcic infections, 3 with streptococcic infections, and 11 with miscellaneous conditions were treated with novobiocin. The daily dose was 2 mg., administered orally. Results in the 75 patients were generally favorable, and they appeared comparable to those obtained with erythromycin. Side-effects were minimal. Maculopapular rashes, which may have been caused by novobiocin, developed in two patients. In five patients with micrococcic wound infection and abscesses, prompt healing did not occur and the infecting organisms rapidly became resistant to novobiocin. For this reason, it is recommended that novobiocin be used exclusively for the treatment of infection caused by organisms resistant to other antibiotics, such as penicillin, streptomycin, and the tetracyclines. Wherever possible, another antibiotic to which the pathogenic agent is also sensitive should be administered simultaneously in an attempt to prevent or delay the emergence of antibiotic-resistant micrococci.

The Treatment of Chronic Granulocytic Leukemia with Myleran. I. G. Early and R. W. Prichard. North Carolina M. J. **17**:315-319 (July) 1956 [Winston-Salem, N. C.].

Myleran is a drug of relatively recent origin that has been found to have a beneficial effect on the course of chronic granulocytic leukemia. It consistently produces a decrease in the number of circulating granulocytes, probably by depressing granulopoiesis. In excessive doses, however, it may cause a decrease in other formed elements of the blood. Thus the chief toxic manifestation is thrombocytopenia. The drug has been shown to be of no benefit in other types of leukemia or in the myeloblastic phase of chronic granulocytic leukemia. Twelve patients with chronic granulocytic leukemia were treated with Myleran in doses of 4 to 12 mg. per day until an adequate effect had been obtained. Good to excellent responses were obtained in seven patients, with remissions lasting up to 13 months. Three patients who had leukopenia, thrombocytopenia, or both were not benefited appreciably by the drug. In patients who responded favorably the first improvement was in the sense of well-being. This was followed by a gradual fall in the leukocyte count, especially in the number of immature granulocytes, together with a rise in the hemoglobin level and a gradual decrease in the size of the spleen. In three patients immature granulocytes completely disappeared from the peripheral blood. After the drug was withdrawn, the total leukocyte count ordinarily started to rise again within from one to eight months. The remaining five patients died. Their survival periods ranged from 1½ to 13 months after the start of therapy. Two of these patients had excellent remissions initially; one also responded well to second and third courses of Myleran, but both subsequently died in myeloblastic relapses. One patient had a minimal response initially but then had a myeloblastic relapse while receiving the drug. Most observers now agree that the method of choice for the administration of Myleran is to give small doses until the desired response is obtained. The advisability of giving maintenance doses after a remission has been induced has not yet been determined. It is not known whether the use of maintenance doses hastens the development of resistance. The one patient in this series on maintenance therapy has done quite well over a period of 13 months. The possibility of a carcinogenic effect should be kept in mind when patients are being treated with this drug. Myleran seems to produce a greater and more consistent response than other drugs used in the treatment of this disease. It is more easily administered than roentgen therapy and has been found to produce good remissions in some patients who have shown little or no response to irradiation.

Clinical and Experimental Researches on a New ACTH Combination with Prolonged Effect. L. Rosa, G. Bergami, A. Bersani and others. Riforma med. **70**:641-645 (June 9) 1956 (In Italian) [Naples, Italy].

The authors studied the effect of corticotropin (ACTH) combined with a phosphate of polyphloretine (AH 51). Local metabolism of ACTH was considerably delayed. The effect of a dose of 20 I. U. per day on 10 patients with asthma lasted 24 to 48 hours. Maintenance dose was 5 I. U. A high dose of 30 I. U. had an effect for three or four days on three patients with urticaria. Eosinophilia dropped to about 50%. The eosinopenic effect lasted from 72 to 96 hours. The administration of one dose of the drug increased the elimination of the 17-ketosteroids. The effects of this new ACTH combination last four times longer than those of plain ACTH for beginning doses; they last eight times longer for maintenance doses. The combination was well tolerated and did not cause side-effects.

PATHOLOGY

Electron Microscopy of the Leprosy Bacillus: A Study of Submicroscopical Structure. E. M. Brieger and A. M. Glauert. Tubercle **37**:195-206 (June) 1956 [London, England].

Mycobacterium leprae and Myco. tuberculosis are indistinguishable in preparations stained by the Ziehl-Neelsen technique. Conclusions drawn from electron micrograms of unsectioned bacilli may be deceptive unless the evidence is supplemented by examination of ultra-thin sections. Since sectioning has given information of a submicroscopic structure in ordinary bacteria, it was hoped that by applying this technique to the study of Myco. leprae it would be possible to decide whether the differences seen in electron micrograms of unsectioned mycobacteria are due to genuine differences in internal organization. It was also thought that the technique of ultra-thin sectioning might give information on the structure of the "globi" or lepra cells, which have been the subject of so much controversy. It was planned to compare the intracellular growth of the leprosy bacillus with that of the tubercle bacillus, which had been studied previously.

Material from six patients with lepromatous lesions and from three with the tuberculoid or macular type of leprosy was obtained at a leprosarium in the Belgian Congo. Tissue juices were embedded in agar and fixed in osmic acid. They were transported to England by air in a 70% alcohol solution and then embedded in methacrylate. Punch biopsies were prepared in the same way. Electron micrograms of leprosy bacilli confirmed observations made on stained preparations, which have shown that the morphological appearance of these organisms varies. The bacilli seen in electron micrograms range from short bipolar rods to filaments of different thickness and density; dense spherical forms are also seen. The relationship of these forms to one another cannot be ascertained from a series of fixed preparations. Nevertheless, if the pleomorphism that is observed is not due to degeneration, the leprosy bacillus must have a complex life history. The leprosy bacilli of the tissue juices occurred as isolated filaments and rods and as groups of organisms or "globi."

There has been considerable speculation concerning the structure of the "globi." According to Denney, four different interpretations have been given. Some observers have considered them to be intercellular colonies; others have considered them to be clumps formed within lymph spaces, mechanically compressed

into spherical or spheroidal forms; still others have expressed the opinion that the masses represent colonies of individual rods bound together as a zoogloea. A fourth view is that they may be characteristic colonies growing within an as yet unidentified membrane. Denney himself agrees with the last view. Chaussinand distinguishes between an "amas," or "mass," and a "globus." In the mass the bacilli are still distinguishable as individual organisms. In the globus the bacilli lie end-to-end, in parallel array, and are so tightly packed that it is no longer possible to distinguish them from one another.

The electron micrograms also show groups of bacilli contained within a limiting membrane that are similar to the globi described by Denney. The nature of this membrane cannot be deduced from the electron micrograms, but the possibility that it is the cell membrane of a disintegrating leukocyte cannot be disregarded. Denney believes that the membrane restrains the growth of the bacilli and Chaussinand refers to the membrane as a capsule and agrees that it prevents the spreading of the rapidly multiplying organisms. It is impossible to judge from electron micrograms whether the bacilli within these clumps are viable, although some have the density of apparently healthy organisms. Under the electron microscope the bacilli confined within these membranes are still distinguishable from one another. The findings reported in this paper are only preliminary. The study was limited to obtaining evidence of the value and possibilities of applying to the problems of leprosy techniques that had already proved valuable in the field of tuberculosis research.

The Failure of Increased Intravascular Pressure to Induce Arterial and Arteriolar Necrosis. D. G. Johnston and G. A. Marples. Angiology 7:279-286 (June) 1956 [Baltimore].

The causative relationship of necrotizing vascular lesions and hypertension has long been a subject of speculation and debate. Opinions regarding the pathogenesis of acute vascular disease in hypertension can be grouped into three general categories: (1) effects of increased intravascular tension on vessels as the chief factor; (2) effects of increased intravascular tension and toxic substances in the blood resulting from renal insufficiency and/or renal ischemia as necessary factors; and (3) effects of toxic substances alone. Investigators and clinicians are accepting more frequently the idea that, in hypertension, arterial and arteriolar necrosis are caused principally, if not solely, by the effects of increased intravascular pressure. The most vigorous proponents of this idea have been Byrom, Dodson, and Wilson. In the experiment of Byrom and Dodson, the major portion of the arterial system was subjected to mechanical stretching of the wall by the forceful injection of fluid.

The present authors decided to subject a small part of the arterial system to rapidly increased intravascular tension. The immediate recipients of the acute hypervolemia, in this experiment, were one or both renal arteries, via a short segment of aorta. Ninety adult male albino rats of Wistar strain were used. Ten of these were controls. It was found that acute necrosis of renal arteries and arterioles could not be caused by sudden severe increases of intra-aortic pressure in the region of the renal ostia. These experiments do not support the "vicious circle" theory of Wilson and Byrom and their contention that necrotizing vascular damage is the direct result of hypertension.

Secondary Amyloidosis in Leprosy. J. S. Shuttleworth and Sister Hilary Ross. Ann. Int. Med. 45:23-38. (July) 1956 [Lancaster, Pa.].

Secondary amyloidosis is the leading cause of death from leprosy in the National Leprosarium of the United States. The primary purpose of the studies described was to find a method of diagnosing amyloidosis at an earlier stage than is possible with the Congo red test. The first approach was to correlate Congo red findings with clinical and autopsy material. The next step was the study of serum protein patterns in kown cases of amyloidosis parallel with controls in an effort to find a consistent pattern that might be of assistance in determining which patients have or will have amyloidosis and also to study the effect of large doses of hyaluronidase on the serum protein pattern, proteinuria, and hepatosplenomegaly in amyloidosis. A third, very limited, study was to obtain liver biopsy specimens with the Vim-Silverman needle in cases of known amyloidosis (as evidenced by the Congo red test) and in cases in which amyloidosis was not apparent. The Congo red test was performed on 95 patients in various stages of leprosy. Eight of these had the tuberculoid and 87 the lepromatous type of leprosy. In some of the patients the test was repeated at intervals of a year. The Congo red was given intravenously in a 1% aqueous solution in dosages of 1 cc. of the solution per 10 lb. of body weight. Blood specimens were collected at the end of two minutes and one hour after the injection, the two-minute specimen being used as the control. Urine specimens were examined for Congo red one hour after the administration of the dye. Laboratory studies ascertained the nonprotein nitrogen content of the blood; the total serum proteins; serum albumin; globulin; alpha, beta, and gamma globulins; serum cholesterol; phospholipids; polysaccharides; mucoproteins; and the function of the liver by the thymol-turbidity and cephalin-cholesterol-flocculation tests. Urinalysis consisted of specific gravity, quantitative albumin, sugar, and microscopic examinations. Serum polysaccharides were determined by the tryptophan reaction and expressed as Coleman units. Mucoproteins were determined by the method of Winzler and others.

The authors record and comment on the results of the various tests and conclude that amyloidosis of the kidney, which occurred in all of the patients, is the direct cause of death. The diagnosis of this complication depends largely on the development of a persistent proteinuria, Congo red absorption, hepatosplenomegaly, and, to a lesser degree, altered serum proteins and perhaps liver biopsy in selected cases. The correlation between the Congo red test and the degree of amyloidosis is poor, and unless this test shows 80 to 100% dye absorption in one hour the diagnosis cannot be made from this finding alone. Serum protein and lipoid changes occur in lepromatous leprosy per se, and in a study of the various protein fractions no consistent alteration occurred in cases of leprosy complicated by amyloidosis. The average duration of life after the onset of proteinuria in amyloidosis was 38.33 months, with a fairly wide range above and below this figure. The development of anemia and a progressive elevation of the nonprotein nitrogen are unfavorable prognostic signs.

The Treated Pulmonary Lesion and Its Tubercle Bacillus: I. Pathology and Pathogenesis. W. E. Loring and H. Mac Vandiviere. Am. J. M. Sc. 232:20-29 (July) 1956 [Philadelphia].

The classic lesion of pulmonary tuberculosis has undergone significant qualitative and quantitative changes as a result of treatment with the modern chemotherapeutic agents. The authors demonstrate this on the basis of observations made in their laboratory on 69 surgical specimens obtained in 11 pneumonectomies, 1 bilobectomy, 24 lobectomies, 28 segmental resections, and in 5 operations combining lobectomy with segmental wedge resection. Studies on these specimens and reports by other observers indicate that the morphological alterations produced by the administration of streptomycin differ from those that result after treatment with isoniazid. The authors describe first the morphological modifications of the classic tuberculous lesion caused by streptomycin and then those produced by isoniazid. They suggest that these changes are probably determined by two different factors: (1) the site of action of the drug with respect to the individual cell, and (2) the action of the drug on the fundamental metabolism of the bacillus. Streptomycin and isoniazid are capable of attacking the tubercle bacillus directly. They materially aid in the prevention of multiplication and slow down metabolic processes, and isoniazid even permits destruction of the bacillus. The pathological evidence presented in this report is indirect. The bacteriological findings described in the report following this one contribute further valuable data.

The Treated Pulmonary Lesion and Its Tubercle Bacillus: II. The Death and Resurrection. H. Mac Vandiviere, W. E. Loring, I. Melvin and S. Willis. Am. J. M. Sc. 232:30-37 (July) 1956 [Philadelphia].

This second report is concerned with two problems. The first concerns the autonomous or drug sterilization, or both, of the tuberculous lesion. The second problem concerns the modification of viable bacilli. Several workers have found lesions within the human body to contain microscopically visible acid-fast bacilli that do not grow on culture mediums. Since this phenome-

non was observed prior to the advent of antituberculous drugs, it cannot be assumed that drugs are solely responsible for this nonculturable status of visible bacilli. Opinions are divided as to whether these organisms are alive or dead. The authors made bacteriological studies on pulmonary tissues obtained in the surgical treatment of 84 patients with tuberculosis. These tissues contained 48 open cavities, 26 closed cavities, 17 end-stage cavities, and other lesions. All patients had received combined chemotherapy for varying periods. When materials from 48 open cavities were placed on culture mediums, growth resulted in the usual period of less than eight weeks in 44 of them. One culture required three months to grow. The cultures were, in general, resistant to one or another of the major antituberculous drugs. From 22 closed cavities, no bacilli grew on culture within the usual eight-week period. In nine instances, however, cultures grew after extended incubation of from 3 to 10 months. Bacilli were found microscopically in 9 of 17 end-stage cavities, but when material from these cavities was placed on culture mediums, there was no growth, even after extended incubation.

Thus it has been demonstrated by bacteriological and pathological (preceding paper) data that in certain lesions tubercle bacilli may be disposed of. This allows the normal body mechanisms and physicochemical status to produce the end-stage cavity. The closed cavity with its hibernating bacilli is apparently the result of normal body mechanisms with little drug effect becoming manifest within the cavity. It was in this type of lesion that extended incubation demonstrated its greatest value by increasing the propagability of the latent bacilli. A high percentage of the classic open cavities revealed rapid growth and the bacilli were generally resistant to drugs. These are interpreted as drug failures insofar as the cavity and its bacilli are concerned.

The authors believe that the whole story is not known, and that, if further enzymes or further improvements of techniques are introduced, more of these bacilli thought "dead" may actually be found to be alive. One type of lesion (closed cavities) has revealed bacillary life where viability was doubtful. There may be other instances yet unknown. There are still bacilli that can be seen but that do not grow with this technique. What will happen to them in the body? Will modified environmental conditions bring them to life? What is the future fate of these adapted tubercle bacilli?

Electron Microscopy of Poliomyelitis Virus. A. R. Taylor and M. J. McCormick. Yale J. Biol. & Med. 28:589-597 (June) 1956 [New Haven, Conn.].

Concentrated poliomyelitis virus preparations containing essentially one type of particle have been obtained consistently from infectious tissue culture fluids by means of a combination of alcohol precipitation and centrifugation. The ultimate size and shape of small virus particles as they are seen in shadowed electron micrographs appear to be dependent upon the hydration of the particles at the time of the first exposure to high vacuum. The authors describe a method for the preparation of electron microscope specimens, in which the collodion membranes are formed on agar blocks, used as filtration membranes for the samples, and subsequently mounted on specimen screens for examination. The use of collodion as a filtering membrane for the preparation and mounting of small pathogenic viruses for electron microscopic examination has distinct practical advantages. The equipment is simple and easily sterilized. The viruses may be handled in saline solutions avoiding the drastic osmotic effects of water and nonisotonic salt solutions. The studies described led to the hypothesis that the characteristic particles of poliomyelitis virus, approximately 30$_{\mu}$ in diameter, are "cell-like" structures containing a central body approximately 20$_{\mu}$ in diameter and a surrounding membrane.

RADIOLOGY

Bronchial Carcinoma: Effect of Radiotherapy on Survival. J. R. Bignall. Lancet 1:876-879 (June 9) 1956 [London, England].

The survival of 207 patients treated by radiotherapy is compared with that of 248 who were not so treated. Of the 207 patients who received radiotherapy, 114 were given an estimated tumor dose of 1,000 to 3,900 r and 93 were given 4,000 r or more. The group that was irradiated and the group that was not irradiated were as far as possible alike in the factors known to influence survival. No patient was known to have extrathoracic metastases when the decision concerning treatment was made. The greatest difference between the treated and the untreated in duration of life from first attendance at hospital was found in those without mediastinal metastases treated with 4,000 r or more: 35% lived a year and 15% two years, compared with 24% and 6% of the untreated. In the patients with mediastinal metastases the differences were less; and the pattern of survival of those treated with 1,000 to 3,900 r was almost identical with that of the corresponding untreated group. There is suggestive evidence that the differences were not due entirely to the variations in selection and random-sampling but were contributed to by the radiotherapy. It is unlikely, however, that radiotherapy caused an increase of as much as 10% in the proportion surviving a year after diagnosis or 5% in those living two years, even in the most favorable cases treated with the higher doses.

Carcinoma of the Posterior Tongue Treated with Radiation. C. L. Marin and J. A. Martin. Radiology 66:835-841 (June) 1956 [Syracuse, N. Y.].

In the period from 1936 to 1950 a total of 120 patients with primary carcinoma of the tongue were seen at a clinic in Dallas, Texas. Forty of these, or 33.3%, had lesions involving the posterior third of the tongue, and they represent the material for this study. Men outnumbered women, roughly two to one. Most patients were in the age range between 50 and 80 years. All patients were treated primarily with irradiation, employing low-intensity radium needle implantation of the primary tumor. Adequate atropinization and local anesthesia are imperative if one is to obtain good access to the posterior tongue for radium needle implantation. As a rule, lesions located in the true base of the tongue are treated by the vertical implantation of needles containing 2.4 mg. of radium distributed in 4 cm. of active length. Tumors on the posterior lateral border and extensions into the floor of the mouth and sides of the pharynx are implanted with needles containing 1.33 mg. of radium in 1.3 cm. of active length. Patients are hospitalized while the radium is in place. Twenty-two of the patients had lymph node metastases. These were treated by interstitial radium implants combined with heavily filtered x-ray therapy with conventional 220-kv. equipment. The over-all five-year salvage rate was 38%. Ten of the 18 (56%) without palpable nodes survived, but only five of the 22 (23%) with involved lymph nodes survived. Radical surgery was never employed as the primary treatment, but secondary surgery was used for removal of sequelae in a few cases. No block dissections were done. The results obtained compare favorably with a salvage of 33% obtained for a group of 120 cancers involving all portions of the tongue treated with a similar technique.

Ultrasoft Roentgen Rays in the Treatment of Hemangiomas: A Follow-Up Examination of 400 Cases of Strawberry Marks and Port-Wine Stains. E. Amdrup and G. Knudsen. Radiology 66:825-834 (June) 1956 [Syracuse, N. Y.].

Four hundred two hemangiomas in 339 patients were treated in the Department of Radiology of the Town and County Hospital, Kolding, Denmark, during the years 1940 to 1952. Three hundred fifteen of these were elevated, while the remaining 87 were flat. The flat hemangiomas in this series were port-wine stains. No cases of purely cavernous hemangioma (the subcutaneous, easily compressible tumor imparting a bluish appearance to the skin) were observed. All of the elevated hemangiomas treated were strawberry marks; these may be purely superficial or may contain a deeper, presumably cavernous element. No distinction between these two types was made in the present study. Histologically, both strawberry marks and port-wine stains are classified as capillary hemangioma, but while the elevated lesions reveal a poorly differentiated endothelium, the cells of the flat hemangioma are of adult type. This explains the considerably higher radiosensitivity of the strawberry marks.

Up to 1943 the tube used was one giving a beam with a half-value layer of 2.02 mm. of skin at 30 kv. and of 1.15 mm. of skin at 20 kv. Most elevated hemangiomas were treated at 30 kv.,

while the thinnest strawberry marks and flat hemangiomas received the softer radiation. Since 1945, the authors have used a tube with a beryllium window, with a focus-skin distance of 10 cm. A few hemangiomas were treated with Bucky rays, usually in fractionated dosage, with 500 r at each sitting. Except in these few cases, a large single dose was given. At present, the authors invariably use a single dose of 800 to 1,200 r. The adjacent unaffected skin is protected by a thin shield of lead foil, 0.1 to 0.3 mm. in thickness, which is sufficient to stop the beam of ultrasoft rays. Flat hemangiomas are irradiated without compression; elevated hemangiomas must be compressed during the exposure. Otherwise the abundant amounts of blood present in these lesions will absorb a large proportion of the ultrasoft rays, resulting in an undue difference in the dose delivered to the surface and that reaching the deeper portions. The therapeutic results in 315 strawberry marks were excellent in 212, good in 74, and unsatisfactory in 27 lesions. In the port-wine stains the results were excellent in 42, good in 25, and unsatisfactory in 19 lesions. The authors conclude that ultrasoft rays are suitable for the treatment of both flat and elevated hemangiomas. They may be applied to all superficial hemangiomas, irrespective of their location. The technique is simple and the administration rapid, requiring a few seconds up to a few minutes. This is an advantage, especially in the case of a young, restless child.

ANESTHESIA

Phantom Limb Pain Associated with Spinal Analgesia. R. A. L. Leatherdale. Anaesthesia 11:249-251 (July) 1956 [London, England].

A 63-year-old man with a history of intermittent claudication over the past five years had had a midthigh amputation of his right leg, the clinical picture in that leg at that time being almost identical with the one now presenting in his left. Two weeks prior to the amputation of his right leg a right lumbar sympathectomy had been performed in an unsuccessful attempt to save the limb. For about three months after the amputation he had experienced phantom limb pain of a burning character in his right foot, but this had never been severe and had long since disappeared completely. When a midthigh amputation of the remaining (left) leg became necessary, a spinal anesthetic was injected into the subarachnoid space, with the patient lying on his left side. The patient was turned into the supine position immediately after the injection, and coincident with the onset of anesthesia he experienced severe phantom limb pain in his right (i. e., absent) foot and toes. It was far more distressing than any similar pain that had occurred after his first amputation.

Spasms of pain in the phantom limb continued throughout the duration of the analgesia, but, as the latter wore off, the sensations subsided. The relief of pain was almost as dramatic as its onset, and there was no recurrence during the four weeks the patient was in hospital. Examination of the stump of the right leg showed a well-healed amputation scar with no tender areas or palpable masses. He died shortly after discharge from a coronary thrombosis.

Hypothermia in the Repair of Interatrial Septal Defects at the State University of Iowa. J. L. Ehrenhaft and J. Moyers. J. Iowa M. Soc. 46:456-461 (Aug.) 1956 [Des Moines].

Twenty-three patients with interatrial septal defects were subjected at the department of surgery of the State University of Iowa to open cardiotomy with the aid of hypothermia. Eight patients had ostium-primum defects in which the lower border of the defect was formed by the rim of fibrocartilaginous tissue at the junction of the mitral and tricuspid valves. The remaining 15 patients had ostium-secundum defects, the margins of which were formed by a complete rim of fibromuscular septal tissue. In 10 of the 15 patients, ostium-secundum type defects were uncomplicated by other lesions. Cooling was accomplished by immersion in ice water. Rectal temperature was constantly recorded by a specially designed thermocouple and recording apparatus. Since there is a further temperature drop of 5 or 6 C after the patient has been removed from the ice bath, the patients were taken from the immersion tub when rectal temperatures had reached 33 C. The lowest resultant temperature was usually 27 C. To restore normal body temperature, reimmersion in warm water (48 C) was necessary at the end of the operation. The anesthetic agent used in all patients was diethyl ether. Premedication consisted of morphine and scopolamine. Induction with nitrous oxide was followed by administration of increasing concentrations of ether until orotracheal intubation could be accomplished. Thereafter, ether concentrations were decreased as cooling progressed, so that almost all patients were given only nitrous oxide and oxygen when their body temperature was below 32 C. Apparently, the combined effects of morphine, nitrous oxide, and hypothermia met the surgical requirements.

The best results were obtained in patients over 5 years of age who had ostium-secundum defects and only moderately elevated pulmonary artery pressures. Older patients up to the age of 48 who were subjected to surgical exploration and closure of the defects also made remarkable recoveries. Two of the 15 patients with ostium-secundum defects died. Of four patients in whom closure of an ostium-primum defect was accomplished, only one survived; the other three died of cardiac failure during the operation or in the postoperative period. The authors' experience in the correction of interatrial septal defects with the aid of hypothermia supports the contention by other workers that open cardiotomy and direct suture in a bloodless field constitutes a good and a relatively safe method. Hypothermia has been found practical and not particularly hazardous to patients having correctable defects. Ventricular fibrillation occurred in 11 of the 23 patients, most commonly after the septal defects had been closed and at the time that circulation was reestablished. If ventricular fibrillation occurred, cardiac resuscitation and conversion to ventricular rhythm and occasionally to sinus mechanism were accomplished in all but two patients by manual compression of the heart and often-repeated electric defibrillation. In two patients with irreparable lesions and pulmonary hypertension, death took place on the operating table.

PUBLIC HEALTH

Certain Aspects of the Microbiology of Frozen Concentrated Orange Juice. E. R. Wolford. Am. J. Pub. Health 46:708-715 (June) 1956 [Albany, N. Y.].

Coliform bacteria are widely distributed in nature. It has been the experience of the citrus product industry that it is impossible to produce frozen concentrated orange juice that is always free of coliform bacteria. The fact that coliforms have been found in orange juice products by most investigators has led to several studies of their source and significance in citrus products. Patrick found coliforms to be associated with scale insects, fruit flies, and slightly decomposed or damaged fruit. No Escherichia coli was found, but in a later study of cultures isolated from frozen concentrated orange juice, Patrick found that Esch. coli made up an appreciable proportion of the cultures. Hays and Riester found that oranges irrigated with raw lake water may frequently harbor Esch. coli.

Further investigations of sources and possible significance of coliforms in citrus products are reported here by Wolford. He presents evidence to show that the presence of coliform bacteria in frozen concentrated orange juice does not necessarily indicate that direct contamination has occurred; coliforms were isolated from fruit aseptically picked into sterile bags, and this fact indicates that some coliforms are among the normally occurring flora in the groves. Esch. coli was isolated from oranges being delivered to concentrate plants; hence the presence of this organism in frozen concentrate need not indicate insanitary practices at the product plant. Packing house wash-tank solutions were found to contain many coliforms, including Esch. coli, and thus may be one of the principal sources of the organism in frozen orange juice products. Surface contamination of fruit-handling equipment was most common where bits of orange pulp had accumulated. Juice and concentrate samples, when positive for coliforms, appeared to reflect the condition of the fruit used rather than sanitary conditions of the juice line. The majority of coliform-positive samples contained less than 10 coliforms per 100 ml.

BOOK REVIEWS

The Lung as a Mirror of Systemic Disease. By Eli H. Rubin, M.D., Professor of Clinical Medicine, Albert Einstein College of Medicine, Yeshiva University, New York. Cloth. $12.50. Pp. 288, with 92 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

This volume alerts the physician to the wealth of information in an x-ray examination of the chest. The lung serves as a mirror of changes in the organs and tissues of the body not accessible to direct examination. About 80 diseases may be associated with the pulmonary lesions described. Though roentgenography is stressed, the differential features of each disease are considered. The pulmonary lesions are described in the light of the physical and laboratory findings, and an effort is made to present the entire disease as mirrored in the chest film. This film assumes increasing importance as a case-finding tool, not only in detecting the pneumonias, tuberculosis, neoplasms, and other primary pulmonary diseases but also in detecting pulmonary manifestations of skin diseases, hemopoietic diseases, metabolic disturbances, and other disorders in the subspecialties of internal medicine. Even surgical abdominal diseases may show evidence of their presence in the chest film. Without adequate appreciation of the primary disturbance, the significance of the shadow may easily be missed. A number of rarities that may become commonplace with more frequent recognition are included. Though roentgenography and its modalities occupy a key position in chest diagnosis, a history, thorough physical examination, and the necessary laboratory tests, including bronchoscopy, bronchography, and, when indicated, lung biopsy, are essential to a diagnosis. With experience, a particular disease may be suspected or diagnosed with a high degree of accuracy by the roentgenographic findings alone. A definitive diagnosis always requires confirmatory evidence. Broadly speaking, pulmonary diseases may be grouped as primary, secondary (emboli, metastatic malignancies, and terminal pneumonias), and concomitant. If the lungs are involved as part of a systemic disease, the symmetrical distribution of lesions, a vascular or perivascular pattern of abnormal markings, and a tendency toward pleural involvement are characteristic. At least 30 abnormal states may lead to miliary or nodular foci. The author of this book performs a real service by calling attention to frequently unappreciated facts.

Bellevue Is My Home. By Salvatore R. Cutolo, M.D., with Arthur and Barbara Gelb. Cloth. $4. Pp. 317. Doubleday & Company, Inc., Garden City, New York; 575 Madison Ave., New York 22, 1956.

During the more than 200 years that Bellevue Hospital has been caring for the sick, it has grown to be an enormous institution. Some think of Bellevue as a miniature city; others say it has been the cradle of medicine in America. It is the only hospital to which four medical schools are attached: Columbia University College of Physicians and Surgeons, Cornell University Medical College, New York University College of Medicine, and New York University Post-Graduate Medical School. Faculty members from these schools exclusively staff this hospital today. The author has been closely associated with Bellevue in various capacities for more than 25 years. He states, "It costs us $17,000,000 to operate Bellevue each year, of which $14,000,000 goes for payroll, $1,360,000 for food, and $1,155,000 for medical, laboratory, and surgical supplies." The author leaves the distinct impression that the 1,000 visiting physicians, 459 interns and residents, 582 graduate nurses, 500 student nurses, and the hundreds of other attendants all embrace the ideal of kind, courteous, and efficient care for all their patients. Many interesting tales of patients and some almost miraculous cures are related. The author of such beloved songs as "My Old Kentucky Home" and "Old Black Joe" was brought to Bellevue in 1864 as an alcohol-ravaged, pitiful, and wasted figure after he had fallen across the washbowl in his room, severely cutting his neck and face. Three days later he died in the ward at Bellevue. This patient was Stephen Foster, and the old ledger showing his admission to the hospital is still there. The American Society of Composers, Authors and Publishers presented a plaque to the hospital four years ago to commemorate Foster's death. A businessman from Memphis, Tenn., now dead, for 20 years annually came to New York and stood outside the entrance to the hospital for a few moments on Jan. 13, the anniversary of Foster's death. Many stories of patients and of some famous physicians who have served the hospital, as well as some medical discoveries that were made within its walls, are recalled. A chapter entitled The Third Phase of Medicine concerns the rehabilitation services. Some chapters pertain to the great work now done by the psychiatric service. The first five chapters of the book are autobiographical.

J. A. M. A. Queries and Minor Notes. Cloth. $5.50. Pp. 334. Published for American Medical Association by C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

In the past the American Medical Association has published three compilations of items from the Queries and Minor Notes department of THE JOURNAL under the title "Selected Questions and Answers." The last of these, published in 1950, covered the period 1943 to 1949. Because of the large demands for volume 3 long after it was out of print and because of requests for a new compilation, the present volume, selected from items published during the 12 months ending June, 1955, has been made available. Selection was based largely on the teaching value, general interest, and timeliness of the items, avoiding unnecessary duplication and matters so highly technical as to be of limited interest. Like the preceding volumes, this one has no index, but the table of contents is arranged for easy reference.

School Health Practice. By C. L. Anderson, B.S., M.S., Dr.P.H., Professor of Hygiene and Health Education, Oregon State College, Corvallis. Cloth. $4.75. Pp. 360, with 29 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

This book was written to provide the what, how, and why of the functional school health program. It is intended to serve as a textbook for student teachers and as a reference for teachers in practice. Its principal sections include a description of the school-age child, including his appearance in health and illness and his physical and emotional development; a discussion of the organization of the school health program; and detailed descriptions of the three major aspects of a school health program—health services, health instruction, and healthful school living. This book is well organized and has an index and an appendix that contain such useful information as resources for health instruction, record and report forms, and means for evaluating a school health program. Unfortunately, the book was prepared without medical or dental consultation. In many places medical terminology is used inaccurately. The suggested relation between educators and physicians does not conform to the interprofessional consensus expressed by the National Conferences on Physicians and Schools sponsored by the American Medical Association. In the section concerned with communicable disease control, the drugs suggested for the treatment of various skin infections and infestations are recommended in a manner that implies their use in the school without local medical supervision. There is only casual mention of the need for interprofessional planning of the school health program among educators and their colleagues in medicine, dentistry, and public health. Thus, student teachers using this as a textbook will get the impression that the school health program is conceived and executed by educators who are privileged to command the services of the other professions in the community if and when they need them. The value of the book would have been materially enhanced if certain statements in the field of health, medical care, and dentistry had been checked for accuracy through professional consultation and if the spirit of interprofessional cooperation in both the planning and the carrying out of school health activities, particularly school health service, had been more clearly delineated.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. [Selected by Noah D. Fabricant, M.D., Editorial Associate, Journal of the American Medical Association.] Published with approval of Board of Trustees, American Medical Association. Cloth. $5.50. Pp. 661. Intercontinental Medical Book Corporation, with Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This compilation of the best of the abstracts culled from the Medical Literature Abstracts section of THE JOURNAL is chiefly concerned with the literature of 1955. The abstracts are not arranged by medical specialties, as they are in THE JOURNAL, but by organ systems, with additional chapters entitled Metabolism, Poisonings, Infections, Therapeutics, and Diagnostic Technics. The value of abstracts in general has long been recognized, and this conveniently arranged volume should be a welcome addition to the library of the busy practitioner. The book has an index.

Medicinal Chemistry. Volume II. Editors: F. F. Blicke and C. M. Suter. Series of reviews prepared under auspices of Division of Medicinal Chemistry of American Chemical Society. By A. Stoll and others. Cloth. $10. Pp. 311, with illustrations. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16; Chapman & Hall, Ltd., 37-39 Essex St., Strand, London, W.C.2, England, 1956.

The second volume of this series is similar in purpose and make-up to the first, which appeared in 1951. The purpose is to provide a comprehensive summary of data on compounds having biological properties and thus to aid in the correlation of structure with activity. Each chapter, written by an authority, includes compounds having specific biological activity. Where it is not feasible, because a category may be too large to include all the information in a single chapter, a subdivision is made on a chemical basis. The present volume contains four chapters dealing with cardiac glycosides, synthetic estrogens, arylpiperidine analgesics, and β-haloethylamine adrenergic blocking agents. Most of the chapters contain a large portion of the material in table form in order to conveniently correlate activity and structure. Each chapter contains numerous references to the original literature.

Diseases of the Skin. By Richard L. Sutton, Jr., A.M., M.D., F.R.S., Chairman of Department of Dermatology, University of Kansas Medical Center, Kansas City, Kan. Eleventh edition. Cloth. $29.50. Pp. 1479, with 1972 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Successive editions of this monumental work have become a standard component of the dermatologist's library. Since the last edition, the co-authorship of Sutton and Sutton has been dissolved by the death of the senior author; but the excellence of the present edition assures the book a continued prominent place in the dermatological literature. This volume is a combination textbook, encyclopedia, and atlas. The organization is that of the traditional textbook, but each section is supplemented with brief reviews of the literature and of pertinent experimental work, descriptions of unusual cases, and extensive bibliographic references with commentary. In addition, each section is profusely illustrated with black-and-white clinical photographs and photomicrographs of outstanding quality and variety. This is an extremely valuable feature of the book. The scope of the work is comprehensive. All known skin diseases, including the exanthems, are discussed and adequately indexed. Diseases are grouped by cause when this is known, and by morphology when it is not. The table of contents clearly indicates the major classifications, but the formidable lists of diseases presented under the last three chapter headings need further subgrouping to facilitate reference. In the text, descriptions of the individual diseases are lucid and complete. The outlines of therapy are practical, explicit, and comprehensive. In some cases the author reviews the literature of therapy without comment; in others, he clearly states his preference. The inexperienced may wish for more critical evaluation, but the more experienced reader will appreciate the wide basis on which to make his own evaluation. The histopathological descriptions throughout the text are occasionally less detailed than the graduate student may wish, but for the most part they give an adequate picture.

In the 13 years since the last revision, there have been many advances in dermatology. These are well reflected in this new edition. Much new information has been included, and the sections on therapy have been thoroughly revised and brought up-to-date. The book is readable and useful. The novice may wish for more synthesis and less reference in some sections, but those conversant with the field should welcome the ready access to the source of each observation and opinion expressed. The inclusion of complete bibliographic references in parentheses within the sentences of the text is distracting but perhaps more useful than the bibliographies in small print at the end of each chapter that are found in previous editions. The book should be most useful to dermatologists and graduate students. It should also be helpful to practitioners and students with some orientation in the field. It is somewhat too large (and expensive) for a beginning textbook in dermatology.

Poliomyelitis: Papers and Discussions Presented at the Third International Poliomyelitis Conference. Compiled and edited for International Poliomyelitis Congress. Cloth. $7.50. Pp. 567, with 442 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 2083 Guy St., Montreal, Canada, 1955.

As stated in the preface of this book, the demand for the published proceedings of the first two conferences was such as to leave no question whether to publish the proceedings of the third conference. The book covers the social aspects of poliomyelitis, medical care of acute cases, infection and immunity, tissue culture of the causative virus, orthopedic aspects of the disease, and physical medicine and rehabilitation. There is also a section on current trends and future prospects, as well as one in which 20 scientific exhibits are presented. The papers, which are by outstanding authorities from all over the world, are attractively printed. Extensive use is made of illustrations, most of which are clear and add to an understanding of the text. There is an index. Current interest in poliomyelitis is far greater than its importance as a public health problem would warrant, and it is to be hoped that modern methods of immunization will make it so rare that some of the attention now devoted to this disease can be directed elsewhere.

Virus Diseases and the Cardiovascular System: A Survey. By Ernest Lyon, M.D. Cloth. $5.75. Pp. 215. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 99 Great Russell St., London, W.C.1, England, 1956.

In the past few years the effects of the many virus diseases on the cardiovascular system have been recognized. Reports of electrocardiographic changes in a number of virus infections, the increasing incidence of nonspecific pericarditis and myocarditis probably of viral origin, and the relationship of rubella (German measles) in the pregnant mother to congenital heart disease in the child have made the internist and cardiologist aware of the cardiovascular problem in virus diseases. Although much has been written on the subject, pertinent information is difficult to obtain because reports are scattered through many different journals. Dr. Lyon, a well-trained microbiologist and clinician, has done a great service in reviewing a large number of articles in order to include in this volume all the pertinent information on the effect of virus diseases on the heart and blood vessels. In the first part he reviews the present concepts as to how the viruses act on the circulation; in the second part the individual diseases and their specific peculiarities are described; and in the third part rickettsial infections are discussed. An extensive bibliography is given at the end of each chapter. This book should be most welcome as a reference book to the internist and cardiologist.

Diseases of the Chest. By H. Corwin Hinshaw, M.D., Ph.D., Clinical Professor of Medicine, Stanford University School of Medicine, and L. Henry Garland, M.B., B.Ch., Clinical Professor of Radiology, Stanford University School of Medicine, San Francisco. Cloth. $15. Pp. 727, with 634 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; W. B. Saunders Company, Ltd., 7 Grape St., Shaftesbury Ave., London, W.C.2, England, 1956.

This is an excellent presentation of diseases of the lungs by two well-qualified men, who were assisted by a few co-authors for some special subjects. The book covers all the usual and unusual diseases of the lungs, bronchi, and pleura. It is beautifully printed, and the illustrations are unusually clear. The bibliography is brief but well chosen. This volume should be of great value to students and practitioners who are interested in diseases of the chest. Its contents are so up-to-date that it should be useful for many years to come.

QUERIES AND MINOR NOTES

TYPHOID IMMUNIZATION

To the Editor:—*In her senior year, a student nurse developed typhoid. This was established by repeated positive blood cultures. She had previously received the conventional three injections of typhoid vaccine in her freshman year and was given one additional injection of vaccine in each of the succeeding years. In the future would it be logical to give typhoid vaccine to her? Does typhoid produce a subsequent immunity in a high percentage of cases? By analyzing the agglutinin response, would it be possible to come to any conclusion regarding future immunity in an individual case?*

M.D., Illinois.

Answer.—It is likely that the patient in question possesses a fairly high level of resistance to typhoid. On the other hand, there is no way to prove this with certainty in a given individual, since serologic tests do not always correlate with actual resistance to the disease. Furthermore, all immunity is relative. Immunity to typhoid is no exception, and the evidence for lasting immunity after an attack of typhoid is not as solid as is the case with certain of the infectious diseases, e. g., measles or mumps. However, in areas where typhoid is highly prevalent, it is usually a children's disease and is much less common in adults, which suggests that infection generally produces immunity. For this and other reasons it may be assumed that the patient has a fairly high resistance to typhoid and therefore she need not receive typhoid vaccine routinely. On the other hand, if she is likely to be heavily exposed to typhoid infection, it would be a reasonable precaution to administer 0.05 to 0.1 ml. of typhoid vaccine intradermally (but not on the forearm, which is hypersensitive to such injections) not oftener than every three years.

EAR INFECTION AND SWIMMING

To the Editor:—*I am a member of a fishing club that owns a 14-acre spring-fed lake. A committee has decided that, to (1) increase the food supply for the fish and (2) reduce the amount of marine weeds, the lake should be treated with fertilizer. They propose to use a commercial fertilizer known as "10-10-10," which, I understand, is composed of 10 parts each of nitrogen, phosphate, and potash. Do you think it is possible that this treatment of the water may cause swimmers to have ear infections?*

J. T. Brennan, M.D., Clarksburg, W. Va.

Answer.—Ear infection from swimming is nearly always in the form of an external otitis, the result of moisture remaining in the depth of the ear canal causing maceration of the epithelium, offering a favorable culture medium for Micrococcus (Staphlococcus) pyogenes var. aureus, Pseudomonas aeruginosa, and, occasionally, Aspergillus mold. The fertility of pond water should in no way alter its bacterial content for swimmers. It has been found that a silicone preparation, which protects the skin of the ear canal from maceration by water, is useful for swimmers who are troubled with external otitis.

FIBERGLAS

To the Editor:—*I would like to learn of the toxic effects, if any, associated with Fiberglas cloth and of the resins and catalyst used to fix and harden the resins, as used in covering boats and in general hobby materials.*

Earl Parsons, M.D., Little Rock, Ark.

Answer.—Fiberglas itself essentially is harmless. Dust from it will not provoke pulmonary fibrosis. Little such dust reaches the lungs, due to peculiar electrostatic properties of the material. Spicules of Fiberglas may penetrate the skin and lead to mechanical irritation often termed "Fiberglas warts." To facilitate weaving and other fabrications, the glass fibers sometimes are lubricated with such agents as Spindle Oil, which, in turn, possesses no significantly harmful properties. The troublesome exposure connected with the shaping of objects such as boats from Fiberglas derives from the synthetic resins employed. Notable in the group are the epoxy resins, which act both as primary skin irritants and allergens. The manufacture and use of epoxy resins involve a complex array of catalysts, plasticizers, activators, and solvents. The number may include ethylenediamine, diethylenetriamine, acetone, ethyl acetate, benzoyl peroxide, tricresyl phosphate, dimethyl phthalate, cyclohexanone, cobalt, naphthenates, allyl glycidyl ether, and others. More than one of these agents, such as tricresyl phosphate, is known to be toxic, but in resin application (not manufacture) practical exposure is unlikely. The amines constitute the chief concern. The entry of the amine radical frequently provides opportunity for the dermatitis and asthma that occur frequently after sensitization, or primary eye irritation from vapors, together with caustic contact damage on any tissue surface. It is possible that the epoxy resins per se, which are epichlorohydrin bis-phenol condensation resins, are relatively nonactive, all damage being attributable to the ancillary chemicals present.

TRANSFUSIONS IN RHEUMATIC DISEASES

To the Editor:—*I am inquiring about the use of blood transfusions in chronic, subacute polyarticular arthritis. I have inquired at our local hospital staff meetings and no one knows anything about it.*

G. E. Ramseyer, M.D., Plaincell, Mich.

Answer.—The transfusion of blood to patients with rheumatic diseases, particularly rheumatoid arthritis, was used more extensively in the past than is currently the case. Various rationales have been proposed. It has been thought that the administration of blood may have a beneficial, nonspecific, or "tonic," effect and in some manner stimulate the formation of antibodies. The transfusion of blood also has been advocated to increase the content of protein in the serum, in addition to supplying red corpuscles and hemoglobin to the rheumatoid patient in whom active stages of the disease may result in hypoproteinemia as well as anemia. The transfusion of blood usually has been favored more for patients who have the acute or subacute and febrile phases of a rheumatoid process. However, recent studies of the anemia of patients with rheumatoid arthritis generally have indicated that, as the active inflammatory process subsides, the values for hemoglobin and erythrocytes increase without specific antianemia treatment, provided the dietary intake of iron and other substances is adequate.

Normal whole blood has been most often used, but variable amounts and intervals have been advocated by different observers. Other techniques proposed have included the use of blood previously subjected to ultraviolet irradiation or blood (or plasma) obtained from pregnant women. The value claimed for these procedures has not been substantiated by the controlled, careful observations of most rheumatologists. In the course of an extensive trial of blood transfused in various manners, it was found that the benefit, if any, has been temporary and usually insufficient to justify the risks and expense involved. The transient benefit sometimes noted at times may be attributed to a mild, febrile reaction that follows the transfusion of blood. At best it would seem that the administration of blood should be considered only as part of a broad general treatment program based on the indications of each patient's condition. The indications for transfused blood should not depend merely on the ability of the patient to afford the procedure or on the availability of suitable donors. Other more effective treatment generally is equally available or more so, and it may be more practical.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

TREATMENT OF TORULAR MENINGITIS

To the Editor:—*What is the latest treatment of and prognosis in torular meningitis? What is the route of invasion into the meninges?*

William T. Cassano, M.D., Brooklyn, N. Y.

Answer.—Torular meningitis, also known as cryptococcosis or European blastomycosis, is a subacute or chronic infection caused by Cryptococcus neoformans (Torula histolytica), a yeast-like fungus. The disease may possibly be derived from an endogenous source. The route of invasion into the meninges is not generally known but is probably from the respiratory tract, which is thought to be the portal of entry. A history of a mild but definite respiratory infection can usually be obtained from patients suffering from torular meningitis. Most of the cases reported have been of the cerebral and meningeal type. The prognosis is usually poor once meningitis is established, because the host is apparently unable to develop any specific immunologic resistance. Carton and Mount (*J. Neurosurg.* 8:143,1951), in a review of 178 cases with central nervous system involvement, found only one case, that of cryptococcic meningitis treated with sulfadiazine, in which the patient could be considered as cured. Eighty-six per cent of the patients died within one year and 70% of these within three months of onset. The central nervous system disease is considered a virulent one. Although several patients were reported alive after two and a half, seven, and nine years, these still showed evidence of the disease, revealing a more indolent, milder, but rarer type of infection.

Acti-Dione, an antibiotic produced by many cultures of Streptomyces griseus, is the latest treatment. Acti-Dione itself has been unsatisfactory in central nervous system cryptococcosis. Only one of four patients with that disease treated with it and followed for one and one-half years was apparently cured with no sign of recurrence. (Carton and Liebig: *A.M.A. Arch. Int. Med.* 91:773 [June] 1953.) These authors, however, in sensitivity studies found that combinations of Acti-Dione with polymyxin B, or with compound 77, were the most potent and acted synergistically. These combinations, for want of a better remedy, perhaps with fever therapy, should be tried first. The result of the treatment may depend on the dose and route of administration. In evaluating the response to therapy, however, it must be taken into consideration that occasionally a patient with central nervous system cryptococcosis may have a spontaneous remission. Whitehill and Rawson (*Virginia M. Month.* 81: 591, 1854) reported a case of a 16-year-old girl with generalized cryptococcosis in which the lymph nodes, kidneys, liver, and spleen were predominantly involved, presenting a clinical picture resembling Hodgkin's disease. She was treated with 4.05 gm. of 2-hydroxystilbamidine given over a 19-day period with apparent cure.

HORMONES AND THE INCREASED GROWTH OF CHICKENS

To the Editor:—*Are hormones rendered inactive and destroyed by heat as in cooking? I have in mind estrogenic hormones as given to chickens and turkeys to increase their growth. I believe Canada prohibits administration of hormones to chickens. Do you know of any other countries that forbid this practice?*

M.D., New Jersey.

Answer.—Three estrogens are being used in the United States to stimulate growth rate in cattle or to increase fat deposition and improve carcass quality in chickens and turkeys. Diethylstilbestrol is administered to cattle either orally or subcutaneously in compressed pellet form. Poultry are usually implanted with diethylstilbestrol in pellet or paste form or are fed dienestrol diacetate in the ration. Cattle respond to orally given hexestrol, or dienestrol, in much the same way as to diethylstilbestrol (*J. Animal Sc.* 14:329, 1955). Assays of edible tissues of estrogen-treated cattle, chickens, and turkeys indicate that, when recommended amounts of estrogens are fed or implanted, the estrogenic activity of the meat or other organs is extremely low or in many cases undetectable. The safe use of estrogens in meat animal production depends on the lack of concentration of these substances in the tissues rather than the destruction of the compounds in the cooking process. The estrogens used are relatively heat stable. Tests with diethylstilbestrol, which has a melting point of about 170 C, show that, in meat to which diethylstilbestrol was added before cooking, the estrogens had approximately the same activity after the meat was cooked to the well-done state (*J. Animal Sc.* 13:138, 1950). In Canada diethylstilbestrol may be fed to cattle at a level not to exceed 10 mg. per day (similar to the U. S.). At present no methods of administering estrogens to poultry have been approved by Canadian food and drug officials.

GLYCOSURIA IN ELDERLY PATIENTS

To the Editor:—*Several male diabetics between 62 and 72 years of age not on insulin therapy and free from urinary sugar for many years have begun to show 0.25 to 0.5% sugar in spite of strict dietary care. In all cases this follows diminished activity due to retirement or to physical causes. Increased activity would not be advisable in most of these men who are suffering from the concomitants of diabetes or other chronic disease. Would administration of small doses of any of the long-lasting insulins be advisable?*

M. D., New York.

Answer.—The presence of consistent glycosuria, although of mild degree, in elderly patients calls for the administration of small doses of one of the long-lasting insulins. Since these patients generally have an elevated renal threshold for glucose, the presence of sugar in the urine means that the blood sugar level is considerably above normal. Hypoglycemia is of course to be avoided, but patients in the older age groups are, as a rule, relatively insensitive to the action of insulin so that this danger is not great. It is suggested that 10 units of isophane insulin or lente insulin be used as a beginning daily dose and that, after a few days, the blood sugar level be determined in the late afternoon, since this is the period at which these preparations are most active. Postprandial blood sugar values of approximately 150 mg. per 100 cc. would be considered safe and acceptable.

TETANUS IMMUNIZATION

To the Editor:—*Would it be advisable to substitute at the time of an injury the use of three 0.5-cc. doses of tetanus toxoid (fluid or precipitated) at two-week intervals instead of tetanus antitoxin in order to prevent serum sickness and anaphylaxis that may occur with the use of tetanus antitoxin?*

Milton Jabush, M.D., Lakewood, N. J.

Answer.—It would be inadvisable to substitute three doses of tetanus toxoid for one dose of tetanus antitoxin at the time of injury in individuals who had had no previous toxoid immunization. The injection of tetanus toxoid at two-week intervals for three doses in an unimmunized patient would produce adequate circulating antibodies against tetanus infection in about five or six weeks after the first injection. This would almost certainly permit the development of some cases of active tetanus with incubation periods of 3 to 14 or more days. The best way to prevent serum sickness and anaphylaxis resulting from inoculations of tetanus antitoxin would be by universal toxoid immunization. In this manner a booster injection of toxoid at the time of injury would recall adequate concentrations of circulating antibodies into the blood stream, protect the patient from tetanus, and eliminate the danger of serum sickness or anaphylaxis from the antitoxin.

REMOVAL OF STAINS ON GIRL'S BACK

To the Editor:—*A Negro girl, aged 25, has a history of acne of the face, chest, arms, and back of 10 years' duration. The pustular lesions have resolved, leaving large blackish stains that have coalesced on the back. These stains now cause her mental distress. Can you suggest any method that would cause these stains to disappear?*

Reuben H. Pearlman, M.D., Pittsburgh.

Answer.—The pigmentation will most likely disappear in time, but, if the young woman is impatient, she might hasten matters by applying Benoquin ointment. This should be done cautiously to avoid contact dermatitis and/or too much depigmentation.